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AN INVESTIGATION OF THE CONDITION KNOWN AS COASTAL FEVER IN NORTH QUEENSLAND: ITS SEPARATION FROM SCRUB-TYPHUS.

By W. G. HEASLIP.

(From the Laboratory of Pathology and Microbiology, Brisbane, Queensland.)

THE undiagnosed fevers of the coastal strip of Queensland which lies north of Townsville have been given many names, the best known of which is coastal fever. Several different diseases which were originally included in this group have now been identified, the last to be separated being leptospirosis. Langan and Mathew (1935) and Unwin (1935) reported that serum from patients with coastal fever agglutinated Proteus XK, and in both papers it was claimed that practically all cases of previously undiagnosed fever were "endemic typhus". However, the wide variation in clinical types reported in these and earlier papers left room for considerable doubt on this point. The description by Derrick (1937) of "Q" fever, which occurs in and near Brisbane and is due to a *Rickettsia*-like organism, suggested that this disease might also exist in North Queensland. At this time relatively little was known concerning "endemic typhus", and Sir Raphael Cilento, Director-General of Health and Medical Services for Queensland, who in the past has both worked at and urged the elucidation of the problem of the fevers of North Queensland, once again suggested that an application for a research grant for this purpose should be made. This suggestion was carried out by Dr. E. H. Derrick, Director of the Laboratory of Pathology and Microbiology, Brisbane, and his application was approved by the National Health and Medical Research Council.[1] Subsequently I was appointed to carry out the work necessary to achieve the following objects:

(i) To isolate the strain of *Rickettsia* responsible for the cases of typhus;[2] (ii) to identify the vector or vectors of the *Rickettsia*; (iii) to discover which of the local fauna act as the reservoir for typhus; (iv) to determine whether "Q" fever exists along the coast of North Queensland; (v) to resolve the nature, cause and epidemiology of any previously unrecognized fevers of this area.

Literature.

One of the earliest references to coastal fever is of interest because it occurs in a report on plague. Burnett Ham (1907) stated that an outbreak of fever occurred amongst cane-cutters camped six or seven miles from the Mossman sugar mill. Mossman is about 950 miles north of Brisbane and fifteen miles from the nearest port; no cases of plague had previously been seen in the district. Plague was suspected, however, because the patients presented a picture of enlarged lymphatic glands, headache and a short-term pyrexia. Fluid aspirated from enlarged glands contained organisms which were considered to be *Pasteurella pestis*, and in 10 of the 60 cases a diagnosis of plague was made. There were two deaths, and the outbreak, which started at the end of January during the wet season and following heavy rain, continued until May. The residents stated that similar outbreaks had occurred previously following very heavy rain. The time, place,

[1] Further grants by the National Health and Medical Research Council enabled this investigation to be continued without interruption.

[2] The term typhus, unless otherwise qualified, is used throughout this paper to indicate that member of the typhus group which gives rise to serum agglutinins of Proteus OXK only.

clinical findings and, in view of recent discoveries, the presence of the *Pasteurella*-like organism, all suggest that the diagnosis should have been coastal fever.

Sir Raphael Cilento (personal communication) states that he had a similar experience while Director of the Australian Institute of Tropical Medicine at Townsville. A case of undiagnosed fever came under investigation and the presence of a bipolar bacillus was demonstrated, whereupon a preliminary diagnosis of plague was made. Further observations, however, revealed that the condition was not plague.

Smithson (1910) appears to have been the first to describe the fever as such; he called it Mossman fever after the town where he practised. His colleague Dr. Clarke, who had recently come from Mount Molloy, a mining township on the inland side of the range, stated that there the condition was known as scrub fever. (This condition was later considered to be dengue fever.) Smithson states that the local residents held that mosquitoes were responsible for the transmission of the fever, a conclusion with which he does not agree, on the ground that no transmission occurred at the hospital where there were plenty of mosquitoes.

Clarke (1913) also referred to the condition as Mossman fever. He gave a good clinical account of the cases he saw there, but separated them from the "totally dissimilar" cases of scrub-fever of Mount Molloy. Clinically he divided the cases into "drowsy", "restless" and "chronic"; it is probable that the patients in the "drowsy" group were suffering from typhus. Of the total, 25% had conjunctivitis and 35% had bronchitis. Clarke also supplied the interesting information that the earliest settlers on the Daintree River, north of Mossman, had suffered severely from the disease, many of the cases being fatal, and that the fever was known amongst the natives before the arrival of the white settlers in 1877. On epidemiological grounds he suggested a mosquito or sandfly as the vector.

Breinl, Priestley and Fielding (1914) began an investigation terminated prematurely by the war. They referred to the condition as endemic glandular fever, concluded that it was probably mosquito-borne, and made some observations on the pathology. They inoculated two monkeys with blood from a patient, but observed only a temporary enlargement of lymphatic glands and a rise of temperature.

The next reference is incidental but interesting. Cilento (1923), in a paper concerning mite-infestation of man, referred to the resemblance between the endemic glandular fever of Queensland and Japanese River fever, and also between *Trombicula akamushi* and the species of *Leptus* in North Queensland.

Wheatland (1924) discussed coastal fever in comparison with an "endemic" sickness which occurred near Sarina, a small town some 450 miles south of Mossman. On clinical grounds he separated the two diseases, and called the latter Sarina or West Plane Creek fever. From clinical and epidemiological features and despite the high mortality rate (20% to 30%), it is probable that most, if not all, of these cases were typhus. (The mortality rate in Queensland at present is probably about 5%.) Wheatland recorded that those affected were not cane cutters, but men engaged in clearing virgin scrub-land, and that many of the field workers were at that time subject to scrub itch, which was caused by a small red mite. He added that there appeared to be no correlation between the incidence of the scrub itch and the fever. There is no record of any recent cases occurring in the locality, which is the most southerly at which the disease has been recorded.

A period of eleven years elapsed before any further direct communications were forthcoming; but during this time Fletcher and Lesslar (1926) reported that the typhus of the Malay States consisted of two types, which could be diagnosed serologically. The patients whose serum agglutinated Proteus OXK were nearly all plantation workers, and in most instances gave a history of preceding bites by larval mites of the family Trombidiidae. Soon after this, according to Langan and Mathew (1935), Paine and Nye diagnosed typhus in North Queensland, but their findings were not published. It was during this period also that another outside report of interest appeared. Anigstein (1933) in Malaya found an association between a highly pleomorphic organism and cases of scrub typhus. He thought that the organisms were cultural variants of *Rickettsia*. From the results of the present work it appears that this organism or one very similar is associated with the local cases of typhus. However, it is also constantly found in the blood of patients suffering from coastal fever, which is not typhus, and the former association appears therefore to be accidental.

Mathew (1934) made a cultural and serological study of ten cases of coastal fever at Tully with entirely negative results.

Langan and Mathew (1935) and Unwin (1935) reported the agglutination of Proteus XK by the serum of patients in the Cairns and Tully districts respectively. In both papers it was claimed that coastal fever was "endemic typhus". This claim is of interest, as it denotes the general similarity of the cases of coastal fever and of typhus, although, on the other hand, wide clinical variations were evident in the papers quoted and are stressed by Langan and Mathew. On epidemiological grounds Unwin concluded that the vector was the scrub mite and the reservoir native rodents. Mathew (1936) later demonstrated that the agglutination obtained was of the "O" variety.

Mathew (1936), working at Cairns, described a fatal case of suspected typhus and performed animal experiments with inconclusive results. Later Mathew (1938) gave a summary of his observations and experiments which had extended over two years. This revealed that up to the end of 1937 the vector, reservoir and causal organism of coastal fever were still unknown. It is possible that Richards and Easton saw the *Rickettsia* of typhus in smears made from the *tunica vaginalis* of inoculated guinea-pigs; the results of this work were indefinite and were not published. I have had great difficulty in finding Rickettsiæ in smears from guinea-pigs, even when the animals were definitely known to be infected. On the other hand, many smears from such animals, especially those prepared from the *tunica vaginalis*, show bipolar bacilli, of which the smallest look very like Rickettsiæ.

General Investigations.

The present work was begun in the latter half of 1938 at Cairns, a coastal town in Queensland nearly 900 miles north of Brisbane. It is roughly the centre of the area in which coastal fever is known to occur. The facilities of the Commonwealth Health Laboratory there were kindly put at my disposal, and permission to investigate all cases of undiagnosed fever at the Cairns Hospital was given by the superintendent, Dr. J. V. Guinane, to whom I am greatly indebted. I am also indebted to Dr. K. L. Unwin, Dr. T. W. Carroll, Dr. R. S. Cohen and Dr. H. S. Harper, the superintendents of the hospitals at Tully, Babinda, Gordonvale and Mossman, all of whom willingly cooperated whenever opportunity occurred. The type of country has been adequately described in preceding papers, particularly that of Mathew (1938). The climate is tropical and the rainfall seasonal. The fauna consists mainly of rats, bandicoots and wallabies. Mites and ticks are prevalent in uncleared areas and mosquitoes are ubiquitous. March flies and sandflies are irregular in distribution both as to time and as to place.

My first aim was to ascertain whether coastal fever and typhus were one and the same disease. The animal experiments were arranged, therefore, to serve the double purpose of giving diagnostic aid and of isolating the strain of *Rickettsia* responsible for the cases of typhus. In the Dutch East Indies Dinger (1933) had found that white mice died after infection with scrub typhus. Wolff and Kouwenaar (1934) confirmed this observation with Sumatran mite fever. Consequently white mice were chosen for my experiments, and Professor E. W. Hurst, Director of the Institute of Medical and Veterinary Science, Adelaide, kindly made a supply available.

At first the procedure was to examine each patient and to obtain a history and a sample of blood. The serum was separated and tested for agglutination of Proteus OXK and Proteus OX19. In most cases the clot was disintegrated by

being forced through a sterile syringe fitted with a large-bore needle, and a small amount of disintegrated clot (usually 0·3 cubic centimetre) was injected by the intra-peritoneal route into each of a batch of white mice. Blood was taken again and the serum was tested for agglutinins when the patient left hospital or, if the stay were prolonged, at regular intervals. In some cases more than one batch of mice was inoculated with clot obtained at different times from the same patient. Whenever it was possible the patient was examined at frequent intervals. Many of the patients were in hospital for a few days only, and obviously were not suffering from typhus; but the serum of some of these was tested again three weeks after the onset of the illness.

Separation of Typhus from Coastal Fever.

None of the first 14 patients investigated gave any indication of having typhus fever. Specimens of serum consistently failed to show the presence of agglutinins, and the inoculated mice did not die. However, Case XV, that of a farmer's wife who lived near Babinda, proved to be one of typhus. The first sample of serum contained no agglutinins, but one taken a week later gave a complete agglutination of Proteus OXK at a titre of 1 in 2,560. Clot from the first specimen of blood had been injected into mice and caused a fatal infection, as did the clot from subsequent cases of typhus. The mice died after about ten days, and the post-mortem findings were similar to those reported by Dinger (1933). *Rickettsia*-like bodies were seen constantly in stained smears of the exudate from serous membranes, and serial passage in mice was carried on without any difficulty. The final proof that the mice were suffering from typhus was obtained recently when an assistant became infected in the laboratory at Adelaide. His serum acquired agglutinins for Proteus OXK, and mice inoculated with his blood subsequently died of typhus; smears from serous membranes of the dead animals showed the usual rickettsial bodies. There was no possibility of the infection having been contracted from any other source than the mice, since the case occurred in South Australia, where natural infection is unknown. The mice originally infected in Cairns had been brought to Adelaide about seven months previously, and the strain kept going by serial passage. These two cities are more than 1,300 miles apart.

MAP I.

This confirmation of the findings of the Dutch workers, together with the negative results in the earlier cases, made it clear that typhus and coastal fever were two different diseases. The typhus investigation thus became a separate one, which is still in progress. Moreover, it was now possible once more to regard coastal fever as an undiagnosed disease or group of diseases, and to continue its investigation along separate and defined lines. The remainder of this paper is a report of the results obtained, which show that the majority of cases of coastal fever constitutes a definite clinical entity.

Investigation of Coastal Fever.

Laboratory and Experimental Work.

Among the first batches of mice inoculated with human clot there were no deaths; but in mice killed for examination it was observed that there was an enlargement of the spleen, sometimes accompanied by a deposit of fibrin on the liver or spleen or both. The increase in size appeared to be variable, but at the end of three weeks the weight was about twice the normal. Whenever a post-mortem examination was carried out, smears were made from the cut surface of spleen and liver, from the peritoneum and, with male mice, from the *tunica vaginalis*. In many of these stained preparations, especially those from the spleen and *tunica vaginalis*, Gram-negative, bipolar-staining organisms of varying size were seen. Those of medium size were very similar to *Pasteurella pestis*. Sometimes, either with these organisms or alone, a large Gram-positive bacillus was present. It was later found that the former were variants of the latter, which was a member of the anthrax group. On passage of an emulsion of liver or spleen from a killed infected mouse similar results were obtained; but usually more organisms were present in the smears from the second passage animal. Several stock mice were killed, as controls, but showed no signs of infection.

Association of the Organism with the Local Fauna.—During the course of this work some 70 rats and seven bandicoots were trapped in various localities in the bush and in the West Cairns swamp. Mr. E. Troughton, mammalogist to the Australian Museum, Sydney, kindly identified these animals and reported that the bandicoots were all of the one species, *Isoodon torosus*, while amongst the rats were specimens of *Rattus rattus, Rattus norvegicus, Rattus conatus, Rattus assimilis, Melomys littoralis, Hydromys chrysogaster* and *Uromys caudimaculatus*. The ectoparasites were collected from these animals and comprised fleas, ticks, lice and mites of many kinds, both adult and larval. Specific identification is being carried out with the assistance of Mr. H. Womersley, entomologist to the South Australian Museum, to whom I am greatly indebted. Blood was collected when the animals were killed, and in some cases clot was inoculated into mice, the procedure being the same as with clot from patients. The contents of an engorged tick taken from a bandicoot were similarly injected into mice.

The first death resulting from inoculations occurred amongst a batch of mice which had received clot from a captured rat. The mouse died in less than twenty-four hours. This event was closely followed by two deaths in the batch injected with clot from a second rat; one mouse died two and a half days and the other five days after inoculation. (Both the last deaths were delayed, since with this organism if the animal survives for forty-eight hours it usually recovers. With typhus, death of the mouse usually occurs on the tenth or eleventh day.) From all these mice both types of the organism were seen in the smears. Cultures were attempted; but when growth occurred the organisms obtained were either cocci or a Proteus-like bacillus. One mouse inoculated from the second rat was killed on the fourth day after the injection, and an emulsion of liver and spleen was passed to healthy mice. Both were dead next morning. One mouse inoculated from the first rat was bled from the tail fourteen days after the injection, and about 0·1 cubic centimetre of blood in a small quantity of citrate solution was injected into each of two healthy mice. One died within twenty-four and the other within forty-eight hours. Both were infected with the bipolar type of organism. The infection rate of the rats and bandicoots is set out in Table I.

The next death followed inoculation of healthy mice with an emulsion of the liver and spleen of a mouse killed fourteen days after injection of the tick-emulsion mentioned above. In the passage animals death resulted within twenty-four hours and a smear of heart blood showed both types of organisms. The passage of material from mice dead for more than a few hours almost invariably caused

TABLE I.
The Results of the Investigation of Captured Rats and Bandicoots.

Animal.	Number Tested.	Organism.		Insufficient Examination.	Remarks.
		Found.	Not Found.		
Rats	65	46	14	5	Only one attempt at culture was made in each case.
Bandicoots	7	5	2	—	

death; the smears from such mice showed enormous numbers of the bacilli, although at this time all attempts to cultivate the latter were unsuccessful.

In several of the captured rats I observed abscesses in the liver or spleen, or both, and areas of gelatinous consolidation in the lungs. Smears from these lesions showed enormous numbers of a small, thin form of the bipolar bacillus. Both types of lesion have been seen in inoculated mice. One mouse given an intranasal instillation of infective fluid died seventeen days later. Both lungs were found adherent to the pleura, and on section were semi-solid. Smears from the cut surface revealed an apparently pure culture of very small bipolar bacilli. Morphologically these organisms were very like *Rickettsia*, but on culture were found to be a variant of the anthrax-like bacillus.

Association of the Organism with Human Patients.—The first death to result from the injection of human inoculum occurred in a batch of three mice which had been given 0·2 cubic centimetre of clot. Only one of the three died as a result of this injection; the smears showed many bipolar bacilli. The second mouse of the batch was killed after thirteen days and an emulsion of liver, spleen and *tunica vaginalis* was passed to two fresh mice and a guinea-pig. The mice survived and were subsequently found to be susceptible to typhus. The guinea-pig died within twenty-four hours with acute peritonitis, pleurisy and the specific bacillæmia. Peritoneal fluid from this animal was rapidly fatal for mice in a dose of 0·05 cubic centimetre. The third mouse was tested a month after the original inoculation and found to be susceptible to typhus. The patient from whom this clot was collected (Case XVII) was thought to be suffering from typhus; but serum taken on the thirteenth day after the onset of illness did not agglutinate Proteus OXK. He refused to allow any further blood to be taken, but the results of the experiments with the mice proved that he was not suffering from typhus. It was found later that mice which recovered from an attack of typhus, or sustained an inapparent infection, were thereafter immune for about two months.

Cultivation of the Organism.—With the onset of the wet season the work at Cairns was interrupted for several weeks while the strain of typhus, isolated in mice, was investigated at the Laboratory of Pathology and Microbiology in Brisbane. During this period further attempts were made to cultivate the bacilli found in Cairns. No typical bacilli could be recovered from the culture media; but in the light of later knowledge of the pleomorphic nature of the organism, it is possible that some variants of it were grown. However, on my return to Cairns clot from a patient suffering from suspected atypical typhus was injected into a batch of mice and a guinea-pig. In addition, direct blood smears were made from the patient, and also smears from the deposit of his centrifuged serum. The results were almost overwhelming. The guinea-pig died within twenty-four hours with the usual peritonitis and bacillæmia; the mice died after ten days from typhus; and the smears all showed both types of the organism, as did those from the guinea-pig. The serological tests from this patient were in accord with the findings in the mice, Proteus OXK being agglutinated at a maximum titre of 1 in 5,120. It was found later that most patients with typhus had a similar double infection.

There was now no doubt that the organisms occurred in the patient's blood, and renewed attempts to cultivate them were eventually successful. The first step towards success was taken when I noticed that a specimen of serum left standing on the bench for three days had become turbid. A stained smear of this turbid serum was examined and appeared as a pure culture of the organism. The specimen had originally been centrifuged and the deposit examined; it was thus known to contain the organism when obtained from the patient suffering from coastal fever. It was next found that if similarly infected specimens of blood, serum or clot were left standing at room temperature (about 23° to 28° C.) for a few days, a profuse growth of the organisms resulted, and these could then be grown on or in any ordinary media. Once growth was established on artificial media it could be maintained, though with difficulty, at 37° C. Anigstein (1933) had similar difficulty in getting his "*Rickettsia*" to grow, and succeeded only when he introduced a procedure which involved leaving the cultures at room temperature for some days.

Nature of the Organism.—The cultivated organism proved to be pathogenic in relatively small doses for mice and guinea-pigs. Rats and rabbits were more resistant. When death did not ensue within forty-eight hours, recovery usually followed. Pathogenicity tended to decrease following cultivation on agar or other solid media; but virulence remained high in serum culture. Great variation in form occurred, and it was not until further research was carried out at Adelaide, that it was finally shown that all other forms were variants of the large Gram-positive bacillus, which is a member of the anthrax group. Serological confirmation of the relationship with *Bacillus anthracis*, and of the variants with the type, was suggested when it was shown that anti-anthrax serum agglutinated a suspension of the Gram-negative bacilli at a titre of 1 in 640. The serum for these tests was kindly supplied by the Director of the Commonwealth Serum Laboratories. An extensive search of the literature has failed to reveal any report of such an organism. Though morphologically similar to the so-called pseudo-anthrax bacillus, the two are sharply distinguished by the type of disease with which each is associated. The detailed results of the bacteriological investigation will be recorded in a separate paper.

With the achievement of cultivation of the bacilli, the original routine procedure was altered slightly. The clot from only those patients suspected of having a double infection was injected into mice; but the broken-up clot of all patients was left standing at room temperature for a period not exceeding five days, and smears of the clot were made and examined daily. This routine applied also to the blood of captured animals. The use of mice to demonstrate the presence of the bacilli in clot was discontinued as soon as it was realized that in Cairns the animals might become infected naturally. Staining was done with carbol-thionin prepared according to the method of Laigret and Auburtin (1938). The dry film was fixed with methyl alcohol, stained for up to one minute, washed for a few seconds with absolute alcohol and blotted. This method of staining demonstrated clearly the bipolar nature of the Gram-negative form, and also showed distinctly the tendency of the large form to contain metachromatic granules. Since it is also eminently satisfactory for staining the *Rickettsia* responsible for the cases of typhus, this dye proved very valuable for routine work. If there was any doubt as to the nature of the organisms appearing in a clot-culture, a smear was stained by Gram's method. When necessary, cultures were made on agar plates and the pathogenicity was tested with mice.

TABLE II.
Data Concerning Patients Infected with the Anthrax-like Bacillus.

Patient.	Sex.	Age. (Years.)	Residence or Occupation.	Duration of Fever. (Days.)	Place where Bacilli were Found.	Comments and Chief Signs and Symptoms besides Fever, Headache, Anorexia and Adenitis.
C.W.	M.	12	West Cairns.	7	Mice, after inoculation.	Vomiting at onset; three brothers have same complaint.
B.M.	M.	5	West Cairns.	7	Mice, after inoculation.	Cough, furred tongue, several similar attacks lately.
J.J.	M.	28	West Cairns.	5	Mice, after inoculation.	Backache, cough, sore throat, injected fauces.
T.B.	M.	28	Farmhand.	9	Mice, after inoculation.	Fainted before admission to hospital; pain over splenic area.
J.E.	F.	12	Near swamp.	16	Mice, after inoculation.	Cough, weakness, loss of weight.
P.B.	M.	62	Farmhand.	9	Mice, after inoculation.	See text, Case XVII.
A.S.	M.	24	Canecutter.	4	Mice, after inoculation.	Backache, furred tongue.
E.B.	M.	44	Road clearer.	8	Mice, after inoculation.	Vomiting, backache, conjunctivitis, furred tongue, rash; possibly mild typhus.
W.M.	M.	20	Prospector.	4	Mice, after inoculation.	Vomiting, furred tongue, conjunctivitis.
J.C.	M.	26	Timber-getter.	7	Blood.	Rash, conjunctivitis, furred tongue.
H.L.	M.	14	Timber-getter.	15	Blood.	Abdominal pain, furred tongue, cough, injected fauces; possibly typhus.
J.G.	M.	4	Near swamp.	Recurrent.	Blood.	Malaise, loss of weight; recurring attacks at irregular intervals during past eighteen months.
P.N.	M.	15	West Cairns.	5	Blood.	Vomiting, rash, backache, throat injected.
E.B.	M.	45	Farmer.	20	Blood and urine.	Weakness, loss of weight, conjunctivitis.
R.K.	M.	26	West Cairns.	7	Blood.	Giddiness, furred tongue, cough.
J.E.	M.	17	West Cairns.	5	Blood.	General aches, rash, liver margin tender.
W.R.	M.	34	West Cairns.	9	Blood.	Sore eyes, conjunctivitis, furred tongue; later cough and rash.
P.C.	M.	23	Farmer.	6	Blood.	Vomiting, throbbing head, tongue furred, rash.
S.H.	M.	25	Timber-getter.	6	Blood and sputum.	Sore throat, backache, injected fauces, rash.
J.M.	M.	24	Travelling in bush.	6	Blood.	Malaise, injected fauces.
T.B.	M.	61	Camped in bush.	19	Blood.	Sore eyes, conjunctivitis, furred tongue, loss of weight.
A.C.	M.	30	West Cairns.	11	Blood.	"Cramps in legs", nausea, slight rash.
W.B.	M.	43	West Cairns.	Recurrent.	Blood.	Malaise, weakness, loss of weight. Recurring attacks at irregular intervals for three years.
M.M.	F.	30	Farmer's wife.	6	Blood.	Vomiting; patchy, papular rash.
N.M.	F.	14	Near bush.	22	Blood.	Malaise, cough, loss of weight.
D.C.	M.	10	West Cairns.	15	Blood.	Cough, conjunctivitis, furred tongue, rash; three brothers have had same complaint.
J.L.	M.	13	West Cairns.	5	Blood.	Vomiting, sore throat, injected fauces, conjunctivitis, furred tongue.
J.H.	M.	52	Timber-getter.	15	Blood.	As preceding patient. Liver margin tender.
R.D.	M.	25	Near swamp.	13	Blood.	Abdominal pain, sore throat, cough, injected fauces.
L.C.	M.	45	Farmer.	9	Blood.	Obscured by complicating bronchopneumonia.
C.F.	M.	12	West Cairns.	11	Blood.	Vomiting, furred tongue, conjunctivitis.
J.R.	M.	23	West Cairns.	4	Blood.	Cervical glands tender, tonsils enlarged; fainted before admission to hospital; similar attack two years previously, but inguinal glands affected.
L.K.	F.	24	Picnic in the bush.	5	Blood.	Malaise, vomiting, rash.
G.S.	M.	37	Farmhand.	4	Blood.	Malaise, conjunctivitis.
B.J.	M.	5	West Cairns.	3	Blood.	Sore throat, tonsils enlarged, conjunctivitis; two similar attacks in last two months.
C.W.	M.	25	Timber-getter.	10	Blood.	See text, Case XLIIc.
R.M.	M.	4	West Cairns.	Recurrent.	Blood and sputum.	See text, Case "R.M."
M.M.	F.	28	Near bush.	10 or more.	Blood.	Nausea, vomiting.
R.N.	M.	36	Farmhand.	21 or more	Blood.	Pain in splenic area, loss of weight.
H.W.	M.	30	Surveyor.	9	Blood.	Furred tongue, spleen palpable, rash. Possibly typhus.

Clinical Observations.

The following data are compiled from the investigation of 40 cases, in which the presence of the bacillus was demonstrated by inoculation of mice and later by blood-culture. Some details of these cases are given in Table II.

Although the cases vary greatly as to both the severity and the duration of the illness, the signs, symptoms and laboratory findings are essentially the same in all. The illness may last only a few days and be mild, or it may last three weeks or more and be severe. Whilst both sexes and all age groups are affected, the majority of patients are male adults—a selection brought about by occupational exposure to infection. The history given by patients admitted to the Cairns Hospital is almost invariably one of two; either there has been exposure to "bites" in uncleared areas, or else the patient is a resident of West Cairns, which lies adjacent to a swamp. Occasionally there has been a history of exposure at a definite time or for a limited time; from these it appears that the incubation period is about ten days. Three histories of this type are given.

CASE XXXII.—A taxi-driver was forced to remain in the bush all night on February 22, 1939, on account of heavy rain making the road impassable. He had to walk some distance for assistance, and was "bitten" by mosquitoes and probably by mites. The onset of his illness was on March 3, 1939.

CASE XLIV.—A retired farmer was compelled to camp in the bush for eleven days without adequate shelter, because of floods. He was very badly "bitten" by mosquitoes. Mites and ticks are prevalent in the locality. His illness came on two days after he returned home.

CASE LX.—A nurse was one of a picnic party in the Mossman Gorge on May 7, 1939. This resort is in typical bush country. Her illness started on May 17, 1939.

The onset is usually abrupt, with fever, headache, weakness and anorexia, although occasionally it is preceded by some days of malaise. The patient may also complain of backache or generalized aches and pains, and frequently nausea is present, which may be accompanied by vomiting. Sore throat is a frequent complaint and is often accompanied by cough. On examination the only constant findings are pyrexia and enlarged lymphatic glands. At first only a single group of glands may be palpable, but later the affection becomes general. Occasionally the spleen is palpable, and the edge may extend to two inches below the costal margin. In some instances the liver edge also may be palpable, and, if so, it is usually tender. Occasionally pain is present round the splenic area, and tenderness may accompany splenic enlargement. The glands are rarely painful and not unduly tender. The duration of the swelling is variable, but diminution usually commences with defervescence. Conjunctivitis is commonly seen at different stages of the illness and is very variable in intensity. Injection of the fauces is seen when sore throat is present, and when accompanied by enlarged tonsils may lead to a diagnosis of tonsillitis. In some cases, more particularly in children, a diffuse macular rash appears a few days after the onset of the fever, which is seen on the abdomen, chest and shoulders. It may extend to the face, back and arms, and may quite easily be mistaken for the rash of typhus or of rubella; like the latter, it fades in a few days. The tongue is usually coated with a white fur and tends to become dry; later it may show a brown fur in the centre while the edges are reddened. The elevation of temperature is of an irregularly continuous type and falls gradually; occasionally the morning reading is higher than the evening one. In one case the period of pyrexia exceeded

three weeks; it may last only two days. In a typical case it is about five days. The pulse rate corresponds to the temperature level or is proportionately lower. There is usually a loss of weight roughly proportional to the severity of the illness. In the few cases in which the blood was examined a lymphocytosis was observed. A specific bacilluria may be present, but gives rise to no symptoms. Normally the organisms disappear from the blood within a few days of defervescence; but in some cases convalescence, usually rapid, is prolonged and the organisms persist. It is thus possible that relapses occur as stated by the earlier authors; but I have seen none. A history of reinfection is quite common, and the interval between alleged attacks may be short enough to suggest relapse. A few instances of chronic or recurring coastal fever have been observed (see the case of "R.M."). What appears to be a specific bronchitis may develop, when the organisms can be recovered from the sputum. Occasionally this acute condition becomes chronic, a sequel which has been mistaken for phthisis. The condition may cause serious ill health, as was seen in the following case.

R.M., a boy, aged four years, was admitted to hospital six weeks before I saw him. He lived in West Cairns and had had "whooping cough" a year previously. Since then he had suffered from a cough, loss of weight and intermittent low-grade pyrexia. The child looked as if he were suffering from severe malnutrition. While he was in hospital his chest was examined by X rays, and the radiologist reported that both hila were enlarged and the glands were swollen and partly calcified; there were numerous opacities on both sides below the hila, and the process was more extensive on the left side. On four occasions specimens of sputum were examined for the presence of tubercle bacilli; in each case the report stated that none had been seen. I examined a smear of sputum and cultivated the blood in the manner described above. Cultures were also made from the sputum. The smear revealed large numbers of the specific organisms, and these were grown from the blood and sputum without difficulty.

Complications of Coastal Fever.—The only complications observed have been pulmonary infections. When bronchopneumonia supervenes the resultant signs and symptoms are evident. A complicating bronchitis is suggested when the sputum is purulent and contains few or no specific bacilli. The occurrence of cases of chronic coastal fever makes it probable that this disease, in the form of an exacerbation, is itself sometimes a complication.

Diagnosis.—In 11 of the 19 cases of typhus investigated, the same organism was recovered from the blood as was isolated in cases of coastal fever. In seven of the other eight cases the presence or absence of a double infection could not be definitely determined. Details of these results are given in Table III. It has been found that more than one culture may be necessary to prove the absence of the organisms. For some unknown reason an attempt at culture from clot may be without result, although a preceding or succeeding one, or both, may yield the organisms. In instances in which it was tested, blood which gave no results on incubation was found to be infective by passage in fertile hen eggs incubated for five days. The method of making the egg inoculations was that described by Cox (1938). The finding of the double infection in cases of typhus makes it impossible at present to draw a full comparison between the two diseases, and probably explains the long-standing failure to separate them clinically. A mild attack of typhus closely resembles coastal fever, although there is only an initial resemblance between mild coastal fever and severe typhus. In the latter, typically, the temperature stays at a fairly constant level (about 102° F.) for ten days· the defervescence is rapid; the pulse is relatively slow; the patient is drowsy and complains little; an eschar or a rash, or both, may be present, the rash appearing on the fifth day; there are complete anorexia and a great loss of weight. In the case investigated the presence of a true eschar has been diagnostic.

TABLE III.

Results of the Investigation of Nineteen Cases of Typhus.

Examination.	Number Examined.	Anthrax-like Bacillus.	
		Found.	Not Found.
Complete	8	7	1[1]
Partial	6[2]	4	2
Agglutination only tested	5	—	—

[1] Two clot cultures were attempted, but the second specimen was obtained two days after the temperature became normal.

[2] In four cases no culture was attempted, but the bacilli were found in inoculated mice. In the other cases only one culture was attempted; in one the clot became contaminated, in the other the blood was collected eighteen days after the onset.

The diagnosis from bronchitis and influenza is difficult only when coastal fever is complicated by a respiratory infection. The history, the type of pyrexia, the presence of general adenitis and retching after an attack of coughing, will suggest a double infection. Moreover, the complicating condition alone would seldom account for the patient's distressed appearance. Examination of the sputum will probably be helpful, but final diagnosis rests on examination of the blood.

In rubella there is tenderness of the enlarged glands; the rash is usually more pronounced; and the illness is usually milder than coastal fever.

In the typical cases there is little difficulty in diagnosis, and a culture of the blood or sputum usually puts the matter beyond doubt. It is a fact, however, that a double infection may occur with other infections than typhus; for example, coastal fever has been seen in a fatal case of leptospirosis, but it has not been seen except when there was a clear opportunity to contract both infections (see epidemiology). Details of three cases are given below. When the accompanying temperature charts are read, it must be borne in mind that the patients had been given antipyretic sedatives.

CASE XVII.—A male farmhand, aged sixty-two years, had been working in the bush recently. On December 2, 1938, the illness came on with fever, anorexia, backache, headache of retroocular type and cough. On December 5, 1938, he was admitted to hospital. Intense conjunctivitis was present. The tongue was furred and dry. The teeth were carious and discoloured; some were missing, others were loose; extensive pyorrhœa was present. General adenitis was present and the liver edge tender. The patient looked very ill. No other abnormality was detected.

On December 6, 1938, a red macular rash was noted on the body and face. The patient complained of nausea. On December 7, 1938, blood was taken; Proteus OXK and Proteus OX19 were not agglutinated by the serum. Three white mice were given 0·2 cubic centimetre of clot intraperitoneally. On December 8, 1938, the rash was more evident. One mouse was dead, and smears from the peritoneal cavity revealed a pure culture of bipolar bacilli. On December 10, 1938, the rash was almost invisible. On December 11, 1938, the headache was better and the patient's temperature was normal all day. On December 13, 1938, blood was taken; Proteus OXK and Proteus OX19 were not agglutinated by the serum. The patient was discharged from hospital.

Subsequent investigation of the remaining two mice indicated that the patient had not had typhus (see text above).

CASE LIII.—A school boy, aged thirteen years, a resident of West Cairns, became ill on April 26, 1939, with headache, "cold shivers", fever, running eyes and sore throat. On April 28, 1939, he was admitted to hospital. His tongue was moist and slightly furred, and he had conjunctivitis; his throat was injected; general adenitis was present, but the glands were not tender. The spleen was not palpable. On April 29, 1939, he vomited. On May 1, 1939, blood was taken; culture from the clot yielded anthrax-like organisms. The patient's temperature was normal all day. On May 4, 1939, he was discharged from hospital.

CASE XLIIc.—A male labourer, resident in West Cairns, aged twenty-five years, had been working in the scrub for five months. He recollected only mosquito bites; he had been returning home each night. On October 16, 1939, he became ill, with rigor, severe headache, sore eyes and "aches and pains". He had been "off colour" for four days before the onset.

On October 18, 1939, he was admitted to hospital, and on October 19, 1939, a rash appeared.

When he was examined on October 20, 1939, his tongue was dry, with brownish fur and reddened edges. His throat was slightly injected; the conjunctivæ were normal. General adenitis was present and the glands were tender. The spleen was just palpable. A macular rash was present on the abdomen, chest and shoulders. A cough had developed that morning. Blood was taken, and bipolar bacilli grew in culture from the clot. The serum gave no agglutination with Proteus OX19 and Proteus OXK. Mice were inoculated with clot.

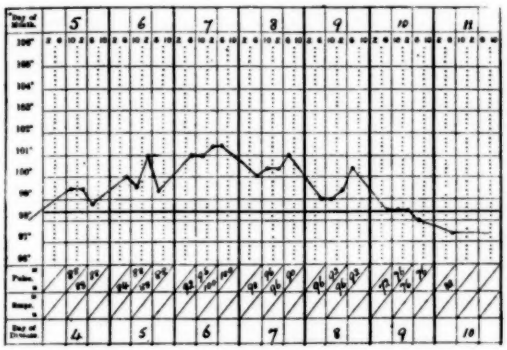

CHART I.

On October 22, 1939, the patient had a rigor at 6 a.m. On October 23, 1939, the conjunctivæ were injected; the rash was gone. Headache was still present and the adenitis was subsiding. On October 25, 1939, blood was taken; bipolar bacilli were grown in culture from the clot. The serum gave no agglutination with Proteus OX19 and partial agglutination at 1 in 50 with Proteus OXK. On October 28, 1939, blood was again taken; the serum agglutinations were as on October 25, 1939. On November 4, 1939, more blood was taken; the serum gave partial agglutination with Proteus OXK at a titre of 1 in 25. The patient was discharged from hospital.

On November 21, 1939, the mice were all still alive; they were killed and examined. No abnormality was detected except for slight enlargement of the spleen.

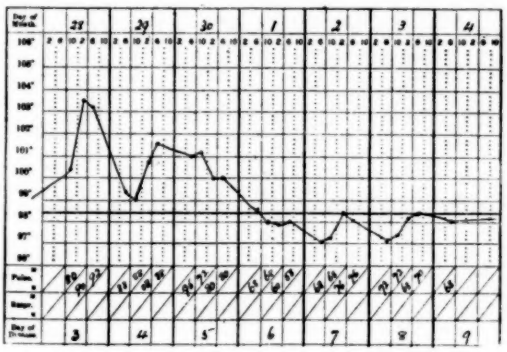

CHART II.

It is possible that in the last instance there was a double infection. The ten days of pyrexia and the rise and fall of agglutinating titre in the serum are very suggestive of mild typhus. Unfortunately, my return to Adelaide made it impossible to carry out further tests with the mice.

Relation of the Organism to Coastal Fever.

After the organism had been found in direct smears of a patient's blood, there was no longer any doubt as to its association with the disease. Owing, however, to the association with typhus and in one instance with leptospirosis, there remained the possibility that it was in all cases a secondary invader. However, after culture of the bacillus was achieved, some 30 cases of coastal fever were investigated and the specific organism was grown from the blood in each case; it also became possible to perform agglutination tests with various forms of the organism in alcoholic suspensions. Specimens of serum from proved cases were found to agglutinate some of these suspensions in titres up to 1 in 160. A few specimens of normal serum were tested and gave no agglutination. These results emphasized the possibility of the organism's having a causal relationship to coastal fever and not being merely

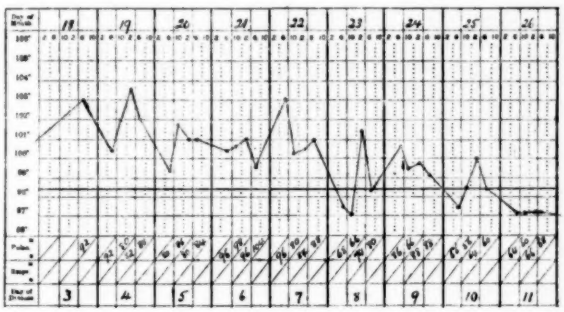

CHART III.

a secondary invader. To resolve the matter I returned to Cairns in October, 1939, and tested the blood of 50 hospital patients, most of whom were suffering or convalescing from some known pyrexial condition. The bacilli were recovered from the cultures in only eight instances. In four of these there was a provisional diagnosis of typhus; one of these patients proved to have the double infection and the condition of one (Case XLIIc) was doubtful. Of the other four cases, one was classed as a pyrexia of unknown origin and in three symptomatic diagnoses had been made—adenitis, tonsillitis and bronchitis. The last case is discussed above ("R.M.").

TABLE IV.

Results of Attempted Blood Cultures from Fifty Hospital Patients.

Original Diagnosis.	Number of Patients Tested.	Number of Positive Results.
Measles	8	0
Tonsillitis	5	1[1]
Abscesses and infected injuries ..	9	0
Pulmonary infections	3	1[2]
Adenitis	1	1[3]
Gastritis	3	0
Other inflammatory conditions ..	2	0
Typhus	5[4]	4
Gynæcological conditions	3	0
Urinary system infections ..	3	0
Non-infected surgical conditions	2	0
Undiagnosed fevers	5[5]	1
Anæmia	1	0

[1] Boy, aged five years. Lived in West Cairns. Two similar attacks previously.

[2] See text for details of this case ("R.M.").

[3] Adult. Lived in West Cairns. Typical case of coastal fever.

[4] Three of the five were from Mossman, one from Atherton, and one from West Cairns. All were adult males who had worked in the bush recently. One from Mossman had typhus, his clot became contaminated, and double infection was not proved. The clot from Atherton was hæmolysed on receipt; no further sample was available. The patient from West Cairns possibly had typhus as well. See text, Case XLIIc. In the other two cases no agglutinins for Proteus OXK developed.

[5] Two of the five were convalescent when blood was taken and were probably suffering from coastal fever. The positive result was obtained with clot from a young woman who lived in the scrub near Mossman and had had a similar attack a year previously. As only one culture was attempted in each case, the other two may also have been suffering from coastal fever.

The details of this study are given in Table IV. The results demonstrate that the organism is associated only with certain defined cases of pyrexia which have been called coastal fever and, as a double infection, with cases of typhus. Although it was thus shown that the organism was not ordinarily a secondary invader, it remained to be proved that it was the actual cause of coastal fever. To achieve this result the disease must be produced in human volunteers by means of the cultured organism. Experiments with this end in view may fail without disproving the causal nature of the organism, because infectivity may be modified by culture or may depend on passage through the vector. Moreover, such experiments are perhaps unnecessary, because of the indirect proof provided by the following evidence:

1. The organisms are constanly found in the blood of patients showing the typical signs and symptoms of coastal fever.

2. When the acute attack of coastal fever is accompanied from the onset by bronchitis, the specific organism is found in the sputum and appears to be the cause of the pulmonary condition.

3. My assistant, who sustained a laboratory infection with typhus, was found to have the usual double infection. The organisms recovered from his blood were pathogenic for mice in the usual way and a suspension of them was agglutinated by his serum, taken during convalescence, at a titre of 1 in 80.

4. There is little doubt that some of the organisms isolated by Anigstein (1933) in Malaya were identical with mine, and he carried out experiments with human volunteers. In this way he succeeded in producing a fever which was very similar to coastal fever and which was, in some cases, almost certainly not typhus as he supposed.

5. A rhesus monkey (*Macaca mulatta*) was given a subcutaneous injection of 0·5 cubic centimetre of infective fluid from a mouse. A week later the monkey was bled and the organisms were recovered by culture from the clot. Another monkey was given an intranasal instillation of a suspension of the organisms in 0·5 cubic centimetre of saline solution, and a few days later developed diarrhœa and mild pyrexia. The organisms were recovered from the blood in the usual way. Neither of these animals showed more than a slight rise of temperature, but both developed adenitis. In three other monkeys given subcutaneous injections of infective fluid the organisms were not recovered from the blood.

6. The organism is regularly recovered from the blood of mice, guinea-pigs and rabbits after inoculation with clot or blood from coastal fever patients, and may be lethal for these animals.

7. What is known of the epidemiology of the disease fits in satisfactorily with the distribution of the organisms in nature, and the latter explains the occurrence of double infections. Thus the cases which occur in Cairns are geographically limited to an area in close proximity to a swamp inhabited by infected rats, and double infections occur only when the patient has been exposed to the possibility of contracting both diseases.

8. That the organism is not a contaminant is shown by the following facts: (*a*) It may be found in direct smears of patients' blood. (*b*) Cultures of blood from 50 hospital patients resulted in the growth of the organism in only eight instances, in each of which the clinical condition was in accord with the cultural result. (*c*) During this investigation practically all specimens of blood have been collected in venules, and on several occasions, when the blood has been several days in transit, it has arrived showing a characteristic purplish-brown colour. On examination the specimen has yielded a pure culture of the bacilli.

9. It has been demonstrated above that the organism is not ordinarily a secondary invader.

The blood of all animals except the mice was, in each case, shown to be sterile before the animal was used for the experiments outlined in this section.

Epidemiology.

In recent years coastal fever has not been in general use as a diagnostic term; usually mild cases have been recorded as pyrexia of unknown origin or influenza, and severe ones as typhus. Consequently there is no statistical record of the prevalence of the disease. Moreover, many patients are not admitted to hospital, and amongst the farming community, most of whom know the condition from experience, a doctor is not consulted unless the symptoms are severe.

As stated above, rats and bandicoots were captured and examined during this investigation. When the animals were killed, blood was collected and cultivated as in the case of the human patients, while smears were made from various organs as in the mice. By this means it was shown that over 70% of both kinds of animals were infected with some form of the anthrax-like bacillus (see Table I). The identity of human and animal strains was later proved in Adelaide. At the same time, mice inoculated with clot from these animals were affected in the same way as those given clot from patients suffering from coastal fever. The same result was seen in mice given the contents of the engorged tick mentioned earlier. These results left no doubt that rats and bandicoots acted as the reservoir for the organism, and at the same time gave a possible explanation of the restriction of the area in Cairns where infection occurred.

These facts, in conjunction with the histories of the patients seen at the Cairns Hospital, are such that a vector found in the bush must be suspected. The three possibilities are mites, ticks and mosquitoes. Although mosquitoes are ubiquitous they must be included, since, *inter alia*, the known animal reservoir could account for the localization of infection to the bush and the vicinity of the West Cairns swamp. The tick must also be regarded as a possible vector since it was possible to find the organism in fed ticks, and also to transmit it from infected to healthy mice by means of "bites" from ticks. For this purpose the eggs of a *Hæmaphysalis humerosa* were brought from Cairns to Adelaide, where the experiment was performed. Moreover, in a series of cases of typhus from an area near Mossman, there was a definite history of tick-attachment preceding the fever, and most of these patients proved to have the double infection. However, a history of tick-attachment in coastal fever is so unusual that the tick could be only an occasional vector.

There is no known evidence against the mite as vector. Its distribution is restricted to uncleared areas and it is usually associated with the transmission of typhus. It has been found that in the coastal area of North Queensland the reservoir for typhus, as for coastal fever, is usually the rat. This apparently is the explanation of the double infection, for even if the mite could not transmit coastal fever, the person who is exposed to mite-infestation is, *ipso facto*, exposed to mosquito or tick "bites". However, it is probable that the mite does act as vector for both infections at the one time. It is reasonable to suppose that what has happened with white mice would occur also with native rats. The following two observations testify both to the persistence of the double infection in mice and to the close association of the bacilli and Rickettsia. First, the typhus strain brought from Cairns over seven months previously, in white mice, had ever since been in Adelaide, where there was absolutely no possibility of the occurrence of natural infection. In that time the blood or pleural fluid from infected mice had been passed serially to healthy mice more than 30 times. Yet when an assistant sustained a laboratory infection with typhus, apparently through a small abrasion on his finger, his blood was found to contain the bacilli as well as the *Rickettsia*. Secondly, when the larval ticks were fed on mice infected with typhus, and subsequently transmitted the bacillus to healthy mice, the contaminated typhus strain had been passed in mice more than 20 times after leaving Cairns.

It is unnecessary for the organisms to pass directly from the mite to the human host. Because of the irritation, the site of attachment is scratched and abraded, and the mite is squashed on it.

The fact that patients give no history of mite-infestation, or if questioned may deny it, is not evidence against the mite as vector. Very few people know what a larval mite is, and still less recognize that it is responsible for the itchy papule that follows attachment. Only when a number of the larvæ attach themselves beneath the clothing, where mosquitoes could not be responsible for the resulting irritation, does the sufferer suspect that he has "scrub-itch". Even when a patient with typhus exhibits an eschar, he is unaware that a mite is the cause of the ulcer, although he can usually recall that it originated as an itchy papule. Reasons for the non-recognition of larval mites are: (i) minute size, (ii) similarity of colour to flesh tints and (iii) the fact that they engorge with plasma and not blood.

Thus it appears that the mite is the most likely vector, both in cases of double infection and coastal fever, and that the vector may occasionally be a tick. It is also possible that the reason why the organism, when first removed from the patient, cannot be cultivated on artificial media at 37° C. until it has multiplied at a lower temperature, is associated with the existence of an invertebrate vector.

The original objection of Smithson (1910) to the mosquito as vector, because no cases of coastal fever occurred at the hospital at Mossman although mosquitoes were there in abundance, can be met on several grounds, one of which has already been mentioned. Nevertheless, this observation is in accord with what is seen at Cairns, and one must conclude that it is unusual for coastal fever to be transmitted directly from person to person. On the other hand, the following evidence suggests that the infection could occur without the intervention of any vector—namely, by droplet infection. First, when the patient has a specific bronchitis the organisms are present in the sputum in large numbers and are easily cultivated. Secondly, a monkey sustained a specific bacillæmia following an intranasal instillation of a suspension of the organisms.

From the standpoint of prevention it is important to note that rats are found in appreciable numbers only where there is adequate food and shelter. These two necessities are afforded by the natural grasses. It is therefore probable that destruction and elimination of grass near dwellings would reduce the incidence of the disease.

That the pathogenicity of the organism is low is indicated by the fact that there is no mortality from human infection. Even when the organisms were seen in the direct smear of a patient's blood, and despite the fact that he was also suffering from typhus, he eventually recovered; it is therefore probable that infection occurs only in favourable circumstances, and does not necessarily result from being "bitten" by the infected vector. On the other hand, many of the patients look decidedly ill, especially in the earlier stages of the disease. Their appearance is probably due to the fact that the bacilli themselves are toxic. Thus a small quantity of the deposit from an old broth culture of the organisms will kill white mice in a few minutes; filtrate from the same culture is not lethal in reasonable doses.

The disease occurs all through the year, but the heaviest incidence follows immediately after the rainy season. At this time there is a seasonal increase in the number of mosquitoes and larval mites, and as a result of the flooding of the swamps and canefields, the rats are driven closer to human habitations and in many instances take refuge in the out-buildings.

During the present investigation cases have been recorded as far north as Cooktown and as far south as Ingham.

Comment.

The data given suggest that there are only two feasible explanations of the constant association of the organism with the cases of coastal fever; either the organism is the cause of the disease or else a double infection always occurs in these cases. The latter explanation is much less acceptable than the former. If a hypothetical virus is the cause of coastal fever, and the bacilli are secondary invaders, one must assume that the vector or the reservoir, or both, are the same for both infective agents, otherwise there is no explanation of the limitation of secondary invasion. Moreover, it would then be probable that most patients with typhus suffer from a triple infection.

With regard to the specimens of blood which sometimes arrive at the laboratory as a culture of the organism, Sir Raphael Cilento (personal communication) states that while he was at Townsville he saw many specimens of blood in venules, sent in for investigation from the northern coastal region, from patients suffering from unrecognized fever, which were hæmolysed on arrival. The condition of the blood was considered to be due to faulty collection and the specimens were therefore discarded. Actually the condition of these specimens is due to the action of the bacilli. They cause some hæmolysis and fairly rapid digestion of the clot. The colour is due to reduction of the hæmoglobin, and there is a characteristic odour like that accompanying decomposition of glue.

It may be worth recording that at Townsville there exists a clinical condition which is locally known as "endemic" dengue fever. This is not reported elsewhere in Queensland and there has not been an epidemic of dengue in Australia for many years. The same diagnosis has been made in regard to certain forms of fever in the Dutch East Indies, some of which are known as Van der Scheer's fever. However, Mertens (1931) maintains that the latter is not dengue, since reinfection could be achieved in such cases if injections of infective serum were used. He was unable to effect mosquito transmission, but found that if mosquitoes were allowed to feed on patients and were then crushed in serum the filtrate of the emulsion was infective. Lack of immunity following a previous attack is one of the features of coastal fever.

It has been mentioned that large numbers of the organisms were found in smears made from animals which had been dead for a few hours. It was subsequently found that rapid multiplication of the bacilli occurs just before or just after death, or at both times—that is, at a temperature less than 37° C. Kouwenaar and Wolff (1934) have reported rapid multiplication of "Rickettsiæ" for several hours after the death of the infected animal. In the course of this work I have examined some hundreds of smears made from mice at varying times after death from typhus, but have failed to observe that the number of Rickettsiæ present was dependent on the time at which the slide was made. It is possible that the authors cited may have mistaken the small form of the anthrax-like bacillus for *Rickettsia*. It is extremely improbable that this organism is confined to the Queensland littoral, and, as has been stated, Anigstein probably isolated the same bacillus in Malaya. Despite features which suggest that there may be a relationship between the bacillus and *Rickettsia*, it is improbable that any exists, since the two organisms are culturally, antigenically and pathogenically distinct.

No cases of "Q" fever have been seen in the coastal region of North Queensland. Specimens of serum from four selected patients were kindly tested by Dr. F. M. Burnet, but they contained no specific agglutinins for "Q" fever. In two instances the patient's condition was not diagnosed. This may have been simply the result of inadequate examination and investigation, but it is possible that there are still cases of fever in this area of which the ætiology is unknown. Only two cases of leptospirosis were seen.

Although no description of an organism corresponding to the one isolated could be found, I have refrained from giving the bacillus a specific name as the bacteriological investigation is still incomplete.

No name has been suggested for the clinical condition described above, since the investigation is far from complete. Although Mossman fever appears to have been the first name published, it was not applied to a single entity and is less suitable than coastal fever, as the condition has a much wider distribution than was at first supposed. Unfortunately, coastal fever, like influenza, has come to be associated with undiagnosed conditions.

Summary.

1. It has been shown that cases of typhus comprise only a small percentage of the previously undiagnosed fevers of North Queensland.

2. After other known conditions have been separated, the residue of the cases of coastal fever appears to constitute a single disease entity. The main signs and symptoms of the condition are pyrexia, adenitis, headache, nausea, weakness, sore throat and loss of weight.

3. Transmission appears to be by a vector which may be a mite, mosquito or tick.

4. From patients presenting the clinical signs and symptoms listed above, an organism which is a member of the anthrax group has invariably been isolated. This organism appears to be the causal agent of the disease, but it is also found in the blood in cases of typhus. It is present in 70% of captured rats and bandicoots.

5. The organism is pleomorphic, but is usually seen as a Gram-negative bacillus showing bipolar staining, or a Gram-positive, anthrax-like bacillus. It grows readily on or in artificial media at temperatures between 20° and 30° C., but will not multiply appreciably at 37° C. when the media are directly inoculated with patients' blood.

Acknowledgements.

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A SURVEY OF ENDEMIC TYPHUS IN NEW GUINEA.

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THE island of New Guinea and its associated groups lie to the north of Australia, roughly between the equator and latitude 10° south. New Guinea and many of the surrounding islands are volcanic in nature; the mainland is steeply mountainous and very rugged, rising in the interior to peaks covered with perpetual snow. The western half constitutes Dutch New Guinea. The southern half of the eastern part constitutes Papua, which is administered by the Commonwealth of Australia, and the north-eastern portion, together with the Bismarck Archipelago and some of the Solomon Islands, is held by Australia as the Mandated Territory of New Guinea.

Since 1930 a form of endemic typhus has been reported from the mandated territory, but so far none is known to have occurred in either Papua or Dutch New Guinea. The main features of the disease are a primary eschar with local lymphadenitis, sustained moderate fever with a relatively low pulse rate, severe toxæmia, enlargement of the spleen, and a typical rash. Clinically it resembles the Japanese river fever, *tsutsugamushibyo*. The serum of patients agglutinates *Bacillus proteus* Kingsbury at moderately high titres, but has no effect on *Bacillus proteus* Lister X19, *Bacillus proteus* X2, or *Bacillus proteus* Warsaw. The disease is practically confined to the white population, and attacks chiefly adult males. Its incubation period is about ten days. The duration of the acute phase is two to three weeks, with one to two weeks of convalescence. The mortality rate is 13% to 19%. Among the diseases which attack white people in New Guinea it ranks second only to blackwater fever in importance.

There is sufficient evidence to show that the likely vector is a larval trombidiid mite, *Trombicula minor* Berlese, 1905, and that a bandicoot, *Echymipera cockerelli* Ramsay, 1877, is probably the effective reservoir of the disease.

Nomenclature.

In dealing with the typhus group of fevers we are particularly unfortunate in the matter of classification and nomenclature. The terms "epidemic", "non-epidemic", "endemic" and "sporadic", as they have been applied to various members of the group, indicate sometimes too much, sometimes too little. In my opinion the use of such specific names is responsible for much of the confusion that now exists. If these terms could be abandoned, if "typhus" were left to signify the classical old world disease carried by lice, and if non-committal names were substituted, such as "paratyphus" for the Brill's disease group (used thus by Balozet in 1936[1]) and "subtyphus" or similar names for the other groups, then we might arrive at a system of nomenclature which would assist rather than hinder a working classification. However, it would require an international committee to decide on such a standard. For some years I have used the term "epidemic typhus" to include not only the classical form, but also its closer relatives such as Brill's disease and *tabardillo*; while under "endemic typhus" I have included such forms as Rocky Mountain spotted fever and the Japanese river fever. This is a terminology which is widely used and understood in Australia, and until finality can be reached I see no advantage in altering it to meet the

requirements of any other system, since there is no other which is not cumbersome, and all are probably just as inaccurate.

In connexion with the Japanese river fever it may be pointed out that Nagayo[2] and Tanaka[3] refer consistently to "the *tsutsugamushi* disease"; the word "*tsutsugamushi*" is used alone only to indicate the Japanese group of actual and potential mite vectors of the disease. Recently, in a Japanese newspaper article[4] giving advance reports on Kawamura's latest work, I noted that the name for the Japanese river fever is *tsutsugamushibyo*.

Confusion also exists in the classifying of these diseases. I prefer Felix's classification according to the main agglutination reactions with Proteus X types,[5] rather than Megaw's earlier suggestion of classifying them according to their vectors,[6] because, as Fletcher has pointed out, "a serological test can be applied with ease in each individual case, but a proven vector can very rarely be found".[7] But there is the difficulty that Felix's three subgroups, the X19, the XK and the undetermined types, cannot be regarded as final, since Zinsser would have us separate "endemic typhus" from Brill's disease,[8] and the flea-borne from the louse-borne types; further, the work of Pijper and Dau in South Africa[9] foreshadows the subdivision of the undetermined group. Felix's XK subgroup, however, seems clear cut and likely to retain its identity; to this group, typified by *tsutsugamushibyo*, the New Guinea form belongs. It is in some respects more closely allied to Sumatran mite fever (the "pseudotyphus" of Schüffner[10]) than to true *tsutsugamushibyo*; but until further investigations can be carried out, it seems preferable to refer to it in general terms only rather than to attach a specific name to it.

Clinical Description of the Disease.

This description is based on a total of more than 100 cases: my own;[11] the series published by von der Borch in 1937;[12] those which I have seen from time to time through the courtesy of Dr. Dickson, Dr. von der Borch, Dr. McKenna and Dr. Giblin in Wau, and Dr. Schroeder in Wewak;[13][14][15] and on notes of other cases provided by these and by Dr. McQueen, Dr. Deland, Dr. Sinclair, Dr. Backhouse and Dr. Spence, from various parts of the territory. How much I owe to all these gentlemen for their keen interest and willing cooperation cannot be estimated. Miss McGuigan, Matron of Wau Hospital, has also given me much valuable information about the many patients who have come under her care.

The disease is practically confined to adult white males whose work involves the clearing of areas of virgin bush or who are occupied in such newly-cleared areas. The onset is sudden. There are no prodromal symptoms, the active phase being ushered in by a chill or a mild rigor followed by a rise of temperature, with headache, malaise and anorexia.

A single typical eschar is present at the time of onset in almost every case. Occasionally an eschar has been observed as early as five days prior to the actual onset of the disease. One patient had two eschars. The usual sites are the ankle, shin, thigh, groin, external genital organs, waistline or axilla; one has been recorded on the eyelid, and one on the breast. Normally the eschar consists of a central tough adherent black slough measuring four to eight millimetres across, surrounded by a dull red areola from two to six millimetres wide. It presents neither pain, tenderness nor itching, and is often unnoticed by the patient. On the scrotum or penis, or in the groin or axilla, it is often modified by moisture and pressure. In one instance it was represented on the calf by a central desquamated area surrounded by a dusky ring of inflammation. The slough dries and drops off during the second week, leaving no scar. In two instances the sloughing extended through the entire thickness of the skin, leaving a punched-out ulcer which remained static until the end of the third week, when it suddenly healed with great rapidity; a firm non-pigmented scar resulted.

At about the time of onset a lymphadenitis, transient and usually mild, develops in the glands draining the site of the eschar. Early in the course of the disease the spleen becomes moderately enlarged, but not particularly tender; it returns to normal size early in the third week.

There are two clinical forms of the disease, the mild and the severe; they differ only in degree, and intermediate stages are often seen. It is convenient to describe the course of the disease in periods corresponding to the first, second and third weeks. General toxæmia, which may be profound, dominates the picture, particularly during the second week. From the onset, frontal headache, slight deafness, anorexia, constipation and mental apathy are the usual features. Terrifying nightmares are common. During the second week these symptoms are intensified, and in severe cases the patient passes into the so-called "typhoid state".

Early in the second week a typical rose-coloured, irregular macular rash appears, first on the trunk, then on the limbs and face. It commences to fade on the third or fourth day after its appearance, but sometimes persists for as long as ten days. It is brighter and more closely set over areas of pressure. It is not followed by desquamation, and leaves no traces behind it. In very severe cases the rash may be urticarial in nature; when this is so, there is usually an associated respiratory reaction resembling hay fever or asthma. In one case the rash was petechial, with relatively large subcutaneous hæmorrhages on the ears and feet.

During the first week the temperature ranges from 100° to 101° F. in the mornings up to 102° to 103° F. in the evenings. The pulse rate ranges from 75 to 90 beats per minute. In mild cases there is little or no change in the temperature or pulse rate during the second week, and from the beginning of the third week the temperature falls by lysis of from three to five days' duration. In some of the very mild cases the temperature falls by short lysis soon after the appearance of the rash, during the second week. In all but the mildest cases bronchitic signs appear during the latter part of the second week. In the mild form this goes no further and clears up spontaneously early in the third week; but in severe cases, particularly in elderly patients, pneumonic consolidation commonly develops by the end of the second week.

In the severe form, even where there are no actual pneumonic complications, the temperature rises a little during the second week, and the pulse rate rises until the pulse-temperature ratio is almost level. When pneumonia supervenes, the temperature ranges about 104° F., and the pulse-temperature ratio becomes very high. Most of the deaths have occurred among elderly patients who were addicted to alcoholic excesses; in such patients myocardial failure develops during the latter part of the second week when the toxæmia reaches its height (rising of the pulse-temperature ratio so that the pulse rate is above the level of the corresponding temperature, before the onset of any pneumonic symptoms, is a sign of bad prognosis), or else it supervenes early in the progress of the pneumonic complications. Occasionally death has occurred at the beginning of the second week in cases in which very severe toxic symptoms developed early, and in which there appeared to be no resistance at all to the infection. Two patients died in uræmic coma towards the end of the second week.

Throughout the active phase of the disease there is a uniform leucopenia; the lowest figure recorded was 3,700 leucocytes per cubic millimetre, but the average is probably about 5,000. The urine remains clear in most cases; it is likely that preexisting renal disease, aggravated by the general toxæmia, was associated with the few patients who showed albuminuria, or who died in uræmic coma.

Once the temperature has subsided, all symptoms disappear and the appetite slowly improves. There is considerable muscular weakness, although there is remarkably little wasting even after severe attacks. Convalescence lasts about ten to fourteen days, but is often interrupted by an attack of malarial fever; this disease usually manifests itself after any period of lowered general resistance, and must be watched for. No permanent disabilities have been noted, even after a lapse of six years in some cases.

The estimate of the incubation period is based on only four cases. One patient had been in a known endemic area for one day only, ten days prior to the onset of the disease; another had been in a similar area on the eleventh and twelfth days before the onset; another on the ninth, tenth and eleventh days; and the last had been in an endemic area for the eleven days preceding the onset of symptoms. It has not been possible to trace any other patients accurately; some had spent months in mite-infested country before acquiring an infection. However, these four cases are in sufficiently close agreement, and they fix the time at about ten days.

Serum Reactions.

The technique used in the Bulolo Gold Dredging Laboratory for testing the serum of patients is as follows.

Blood is drawn from a vein with aseptic precautions, and is placed in the ice-box until the clot has separated; the serum is then drawn off. Any surplus serum left over is mixed with an equal part of acid-free glycerin and stored for checking emulsions and technique should the need arise later. When blood has to be sent from a distance, the usual practice is to collect it in a Behring "Venule" and to place it in an ice-box for at least half an hour before it is dispatched. Because of the excellent aeroplane services in New Guinea, specimens of serum collected in the morning have travelled three or four hundred miles, been tested that evening, and the result has been notified by radio next morning.

Once the serum is ready a series of dilutions in normal saline solution is put up. The same long, fine-drawn pipette, fitted with an India-rubber teat, is used throughout each test, to ensure uniformity of the size of the drops. From five to ten diluting tubes are set out (the number chosen depending on the estimation of the probable titre, judged from the clinical notes provided); into the first are counted 36 drops of saline solution, and into each of the others 20 drops. For each bacillary emulsion to be tested, a series of agglutination tubes is set out, with an extra tube for the control test. Into the control tubes are counted five drops of saline solution. Then four drops of serum are added to the first diluting tube (this gives a preliminary dilution of 1/10). Thorough mixing is ensured by filling and emptying the pipette five times; then 20 drops are transferred to the second diluting tube, and five drops to the first of each series of agglutination tubes. The pipette is emptied, the contents of the second diluting tube are mixed, 20 drops are transferred to the third diluting tube, and five to the second of each series of agglutination tubes. This is repeated until the series is completed. Then the pipette is thoroughly washed with saline solution, and five drops of the testing emulsion are added to each of the agglutination tubes and to the control tube. The final dilutions of serum in the agglutination tubes are thus 1/20, 1/40, 1/80, and so on, while the control tube contains no serum, but only saline solution and bacillary emulsion.

Although this procedure sounds complicated, it is really quite simple in practice, and has several advantages. If a large number of drops[40] is used for mixing each time, any mistake of one or two in the counting of the drops can result in only a relatively small error in the final dilutions, while a sufficient quantity of each dilution is available for conducting tests simultaneously against as many as four different emulsions; and if each mixture is transferred to its several destinations at the one handling before going on to the next dilution, several series of agglutination tubes can be quickly prepared without any chance of variation or multiplication of errors, and time can be saved because the pipette does not need frequent washings.

The agglutination tubes, after being flicked with the finger to mix their contents, are placed in a water-bath and maintained at a temperature of 37° C. for two hours. (For use in hot climates, a simple water-bath whose temperature can be maintained by an adjustable electric light bulb was described by me in 1935.[39]) The tubes are then removed and allowed to cool to room temperature for about twenty minutes, after which the degree of agglutination at successive titres is recorded. If any sign of agglutination is apparent in the control tube, the test is discarded and repeated after all solutions and technique have been checked.

The bacillary emulsions used in 1934 and 1935 were standard emulsions of *Bacillus proteus* Kingsbury, *Bacillus proteus* Lister X19, and *Bacillus proteus* Warsaw, supplied by the Commonwealth Serum Laboratories. In 1936, Dr. Backhouse, of the Public Health Laboratory at Rabaul, sent me subcultures of Kingsbury and Warsaw strains which he had obtained from Kuala Lumpur, and I made up my own emulsions from these, subculturing on nutrient agar. While I was absent on leave in 1937 my Warsaw strain died, and the "O" Kingsbury degenerated to the "H" form. Living cultures imported from Australia failed to grow; Kingsbury emulsions from Australia and Rabaul all gave reactions at lower titres typical of the "H" form; and another culture from Rabaul proved also to have degenerated. Hence, during the latter part of 1937 and the early part of 1938, tests were confined to confirmatory reactions with "H" emulsions. Then, after I had plated out several times, an "O" form of Kingsbury was separated, and a satisfactory Warsaw culture was obtained from Rabaul. In 1939, Dr. Backhouse obtained a culture of *Bacillus proteus* Lister X2, and sent me a subculture. In the assessment of the value of the tests for diagnosis and prognosis, only those carried out with "O" forms have been considered. Reactions with the "H" form of *Bacillus proteus* Kingsbury were rarely positive at 1/20 before the tenth day, and never ran higher than 1/320, even by the end of the third week. They are therefore of no practical value for early confirmation of diagnosis or for estimating prognosis.

A series of agglutination tests at very low titres against *B. proteus* Kingsbury, *Bacillus proteus* Lister X19, and *Bacillus proteus* Warsaw was carried out on healthy white men and natives. It was found that the results obtained at titres of from 1/4 to 1/10 were irregular and quite unreliable for all three organisms, but that a uniformly negative result was obtained at 1/20. This titre was therefore selected as the lowest to be used in all tests.

Tests made on patients suffering from the clinical manifestations of the disease gave the following results: In no case was any agglutination apparent at titres of 1/20 or higher for *Bacillus proteus* Lister X19, *Bacillus proteus* Lister X2, or *Bacillus proteus* Warsaw, but there was a positive reaction against *Bacillus proteus* Kingsbury in every case but one (a patient with all the signs and symptoms of the disease in their severest form, who died on the sixth day, before any agglutination reaction could be expected). A comparison between the stage of the disease and the height of the titre revealed the following facts:

1. Results of tests made during the first week of the disease were inconclusively negative; therefore it is preferable to wait until the eighth day before testing.
2. At the beginning of the second week a positive reaction at a titre of at least 1/80 was usually found. This titre, at this stage of the disease, was therefore adopted as the standard of diagnosis.
3. During the whole of the second week the usual titre ranged from 1/80 to 1/320; during the third week it averaged 1/1,280; during the fourth week it ranged from 1/640 to 1/1,280; from the fifth week it dropped more rapidly; at the fortieth day it averaged 1/160; and no reaction at 1/20 or higher has been found after the fifth month.
4. The maximum titre observed was 1/5,120. The period of maximum titre is actually from the eighteenth to the twenty-third day.

The relationship between the height of the titre and the severity of the symptoms follows along certain standard lines. In exceptionally mild cases, titres of the order of 1/40 at the eighth day, and 1/80 at the twelfth, were usually found. Apart from these, it has been consistently noted that the height of the titre was inversely proportional to the severity of the symptoms.

Subsequent tests on preserved specimens of serum have shown that they retain the power to agglutinate *Bacillus proteus* Kingsbury at about half their original titres after many months.

From these data various inferences can be drawn; the more important are these:

1. Comparison between the patient's titre and the average for the same stage of the disease affords some indication as to how much resistance is being put up; except in the extremely mild form, a lag behind the

average titre can be taken to indicate that the patient is not resisting the infection very strongly; and the reverse applies.

2. The relationship between the severity of the symptoms and the height of the titre, combined with the indicated strength of the resistance, gives a valuable basis for estimating prognosis. I have made the arbitrary assumption that a titre of less than 1/40 at the eighth day, or of less than 1/160 at the twelfth day, indicates a degree of resistance which is dangerously subnormal; when this occurs in patients showing very severe symptoms, or in elderly patients (especially if there is any reason to suspect alcoholic excess), the prognosis is bad; but when it occurs in robust patients who present symptoms of only moderate severity, the prognosis is good; when the titre is equal to 1/80 at the eighth day, or 1/320 at the twelfth, even in patients with severe symptoms, the prognosis is not bad; while if this standard is bettered at these times, the prognosis is excellent, even if the symptoms are very severe. Estimates of prognosis made on these premises during the last two years have proved to be almost invariably accurate.

3. That the titre increases during the first part of convalescence, and then falls rapidly, suggests that since the usual titres to be found during the second week, which is the period of maximum toxæmia, average only 1/160, then serum taken from a convalescent patient during the period of maximum titre, when the range is from 1/1,280 to 1/5,120, should be of value for treatment. Secondly, convalescent serum taken after the fourth week is likely to have such a low titre as to be of little value. Unfortunately, cases of the disease have been so scattered that it has not been possible to apply a practical test of this suggestion so far. It is proposed, should ever two patients be available together at the requisite relative stages, to test the titre of the recipient's serum on three successive days, then to inject a measured amount of serum of known titre; if the recipient's serum is tested daily after the injection, any change in the level of the titre, or in its rise as compared with the average curve, may be observed.

4. In a paper read before the Sixth Pacific Science Congress in 1939[17] I offered the suggestion that, since even my roughly preserved and casually stored specimens of serum retained their agglutinating power *in vitro* for much longer times than did the serum of the same patients *in vivo*, convalescent serum taken at the period of maximum titre might be stored against future need, when it might be of value for treatment. Professor Ludwig Anigstein, in the discussion which followed, stated that the same conclusion had been reached some years ago in Malaya, and convalescent serum was found to have some therapeutic value; but it was found that while stored serum retained its power to agglutinate *Bacillus proteus* Kingsbury, it lost its therapeutic value rapidly; the results of this investigation were not published, but Anigstein regards them as conclusive.

5. The previous point has some bearing on the question of the relationship between the Rickettsiæ and the Proteus group. That the agglutination titre against the latter is a measure of the patient's resistance to the rickettsial infection, is undoubted, and has led to the suggestion that the relationship may be pleomorphic rather than symbiotic; but the fact that, *in vitro* at any rate, the Proteus reaction persists while the therapeutic value of the serum declines, would indicate rather that the two reactions are dissociated, as would be expected if the relations between the two groups of organisms are merely symbiotic.

6. Since patients' serum, after five months, shows no reaction, it was assumed that no permanent immunity is derived from an attack of the disease. Although this does not follow, because of the dissociation of the two reactions, the actual fact was proved in February, 1939, when a white man who had had an attack of endemic typhus in August, 1934, developed the disease again. His second attack ran the usual course of a mild infection, without any apparent variation.

7. As an outcome of the previous point, it seems obvious that there can be no likelihood of developing an antiserum useful for treating the disease.

Does the Disease Occur in Natives?

The important question as to whether the disease occurs in natives requires much further investigation. De Rook, in 1938,[18] stated that endemic typhus did not occur in Dutch New Guinea. In 1939, Dr. F. J. Williams, Chief Medical Officer of Papua, forwarded to me (in a personal communication) the information that while no instances have been observed in white men, among natives there have been several cases of an undefined fever showing some of the features of endemic typhus; clinical details were not available, no confirmed diagnosis was made, nor were post-mortem examinations or laboratory investigations undertaken. Recently, Dr. C. M. Deland wrote to me as follows:

> . . . In 1930 I saw in a mountain village near Kieta [Solomon Islands] an outbreak of a fever that I am sure now was this disease. I am certain that it is far more common than has been realized in natives, and that it presents all stages of virulence from the excessively mild type above to the fatal type.

Notwithstanding these opinions, which should receive the most weighty consideration, I must point out that for six years I have searched unsuccessfully for an authentic case of the disease. At Bulolo are employed 2,000 natives collected from all parts of the territory. Every patient in the native hospital who has suffered from pyrexia of unknown origin, or who has presented any symptom complex even remotely resembling that of endemic typhus, has been thoroughly investigated, without the discovery of any serological or adequate clinical confirmation. Serum from a few possible cases sent by von der Borch and McKenna from time to time also gave negative results. Subject to the proviso that natives may perhaps develop the disease without acquiring a simultaneous symbiotic infection by Proteus organisms (which is not the experience of observers in other parts of the world), there is no serological proof that the disease occurs in New Guinea.

Since cases have occurred among the first white men to penetrate newly opened country, it seems that the disease was already established there, rather than that it followed the white man in; however, as it is primarily a disease of rodents, and does not depend on any human intermediary for its continuance, this is quite feasible, and has not necessarily any bearing on the question of its occurrence in natives.

That there is little likelihood of the existence of any acquired immunity is suggested by the fact that among white men reinfection is possible. Besides, the presence of acquired immunity among adults presupposes the widespread presence of the disease among the children; but it does not so occur.

Turning to the epidemiological aspect, there is no doubt that most natives, and many white men, normally do not suffer from the attacks of mites. It has been suggested that peculiarities of body odour or of skin texture are responsible for this; but among white men, in my experience, neither complexion nor type of skin makes any difference. Since the mites prefer sites where clothing exerts pressure, it is probable that the wearing of loose light clothes may help to reduce their attacks, in which case natives have a considerable advantage over white men. But although I am not able to offer any other explanation, I feel that these points are not sufficiently strong, and do not solve the problem of the apparent immunity of natives to the disease.

In the Dutch East Indies the mortality rate from Sumatran mite fever is 40% among Europeans, but only 5% among the Javanese.[19] This indicates an extremely high degree of racial immunity among the latter, and that this exists for such a closely related disease encourages me to postulate a complete racial immunity against endemic typhus among the primitive Melanesians of New Guinea.

Diagnosis and Treatment.

A diagnosis of malarial fever is usually made at the onset of the disease, and is often only revised when, after two or three days, there is no response to antimalarial treatment. A relatively low pulse rate in a patient apparently suffering from malaria should always be

regarded with suspicion; and this, with persistent fever and frontal headache, should cause a search to be made in the usual sites for an eschar. Dengue fever presents another possible source of error, but the typical bone pains of this disease are not likely to be confused with any of the symptoms of endemic typhus. The low pulse-temperature ratio of amœbic abscess of the liver may cause confusion, but this condition has not the acute onset of endemic typhus, nor is there much resemblance between the symptom-complexes. The leucocytosis of one and the leucopenia of the other would alone serve to differentiate them satisfactorily.

In searching old hospital records, McKenna found quite a number of cases, entered as "typhoid fever", which were undoubtedly endemic typhus. The two diseases have so much in common that in the absence of an eschar it may be necessary to wait until the eighth day, when agglutination reactions may be obtained, before a definite diagnosis can be reached. It should be laid down as a fixed rule that no diagnosis of enteric fever should be made until an exhaustive search has failed to locate an eschar. Even then the diagnosis must be confirmed later by serological tests.

Treatment is general; the main points are a light nourishing diet, good nursing, with special attention to keep the bowels well open, expectant treatment when pneumonia is likely to supervene, and the avoidance of all unnecessary cardiac fatigue from the beginningg. In view of the stuporose state, depressant drugs should be avoided. Digitalis is likely to be dangerous if given before the end of the second week; even after that, moderate dosage may sometimes produce a comparatively rapid and strong effect. Once the disease is established, excision of the eschar has no apparent effect on its progress; this was proved when von der Borch and I excised the eschar in alternate patients; in neither series were we able to discern any alteration in the course of the disease.

The possible value of convalescent serum has been discussed. Babalian[20] has described six cases in Persia in which "autohæmatotherapy" was used successfully; he injected intramuscularly 10 to 15 cubic centimetres of the patient's own blood. This has not been tried in New Guinea, but McKenna has used transfusions of whole blood from convalescent patients; he records no conclusive results. Sulphanilamide has no effect on the disease itself, but is valuable for treating pneumonic complications.

Distribution in the Mandated Territory.

Cases of endemic typhus have occurred in almost every part of the Territory. In the following list (Table I), one was reported by Sinclair from New Britain in 1930;[21] several, collected from the goldfields, were treated by Spence in Salamaua in the same year; the remainder have occurred since December, 1931.

TABLE I.

District.	Cases.	Deaths.
Morobe District:		
Wau area	69	12
Upper Watut area	5	0
Bulolo-Bulwa area	8	0
Ramu area	3	1
New Britain:		
Kokopo-Bita Paka area	3	2
Madang District:		
Madang area	2	2
Karkar Island	1	1
Western Islands	1	1
Sepik District:		
Green River area	1	1
Maprik area	2	0
Aitape area	1	0
Wewak area	3	0
Siling River area	6	0
Totals	105	20

From these figures, it appears that of a total of 105 patients, 20 died, a mortality rate of 19%; but when all the available records are checked, it is obvious that only the more spectacular cases have been accurately remembered from the years previous to 1934, and most of these were fatal. If only those cases are included which have occurred in the Morobe district since August, 1934, when accurate records were commenced, the figures are as follows: total cases, 70; deaths, 9; mortality rate, 13%; which is probably the most reliable figure obtainable. It must be recognized, however, that this applies to patients within reasonable reach of hospital treatment, and that among men working in outlying districts, where no assistance of any kind is available, the mortality rate would be much higher.

Of the 105 patients listed above, 10 were women; one died; two of the others were pregnant, and both aborted. Two were children—one a white boy, aged eleven years, the other a Chinese girl, aged ten years (the only case not among white people); neither was seriously ill.

When the cases from the Wau-Watut areas were analysed (these areas were chosen because they are similarly situated as regards climate, total population figures are easily obtained, and they are served by the one hospital), it was found that the incidence of endemic typhus compared with the total white population and the number of patients admitted to hospital (obstetric patients excluded) was as follows:

Mean population, 1934-1939	1,121
Total hospital patients, August, 1934, to May, 1939 (obstetric patients excluded)	1,307
Total endemic typhus patients, same period	46

From these figures it will be seen that the incidence of the disease is one case per 115 members of the population, and one case among every 27 patients admitted to hospital.

The annual incidence in the Morobe district has been: 1934, 14; 1935, 9; 1936, 9; 1937, 8; 1938, 5; 1939, 17; January to June, 1940, 14. The incidence, month by month, in these areas was evenly distributed, and bore no apparent relationship to rainfall or temperature.

The restriction of the disease almost exclusively to adult males is occupational; bush workers, miners and surveyors are the chief sufferers.

A Larval Mite as the Vector.

The other members of the XK subgroup are all mite-borne, and no other vector is known within this subgroup. Hence the assumption that the vector in New Guinea is a larval mite is a reasonable one. In support of this, there is first the evidence of the site of the eschar. Larval mites abound in New Guinea; they are picked up by man as he brushes against vegetation, or when he sits on logs or stumps; they attack the parts of the body where the clothing exerts pressure—around the waistline, beneath the stocking, on the scrotum and penis, and in the groins and armpits. These are precisely the sites where the eschar appears.

Next, the mites are definitely regional in their habitat. The grassed hills and the drier, less dense bush on the mountain slopes are practically free of them, while the dense, damp jungle of the river basins and the smaller valleys is very heavily infested; sago-palm and water-bamboo swamps are reputed to be the worst spots of all. The felling and clearing of the bush in infested areas bring out the mites in enormous numbers. In almost every case of the disease patients gave a history of having recently been in newly cleared areas, and in most cases in which checking was possible these areas have been found to be infested with mites.

Although ticks abound, no patient has ever given any history of a previous tick bite. During nine years in general practice in Bulolo I have not seen any patient suffering from a tick bite, although I have heard of two cases. There has been no history of preceding pediculosis or of infestation by fleas in connexion with any case so far recorded. Nevertheless, it must be admitted that there is on record no actual history of a preexisting mite bite at the site of an eschar; not that this invalidates the argument, which depends not on the presence of previously noticed bites, but on the probability of previous infestation

by arthropods which might act as vectors. Mites attack man freely in the regions where the disease is endemic at all seasons; why hundreds are bitten each year, but only a few contract the disease, has a natural explanation which will be given in its place.

Apart from other considerations, mosquitoes, sandflies and March flies can be simply eliminated because the eschar appears for the most part in sites not accessible to them. Ticks attack man hardly at all—certainly not commonly enough to account for the number of cases of endemic typhus which occur. Body lice and head lice are unknown among the white population, although I have seen several patients with crab-lice; infestation by the latter must certainly have been a prominent feature in the history of patients if they were the vectors. Occasional transfer of an infected louse from a native to a white man would be the only possible way in which lice could enter into the picture—obviously an untenable solution, in view of the epidemiology of the disease. Just as obviously, fleas from domestic pets merit no discussion. Every few years a plague of tiny sand fleas breaks out, lasts a few weeks, and then subsides entirely; these fleas attack man voraciously (I have seen over 20 at the one time on a child's legs), but again there is no agreement with the epidemiological facts. Some of the bush rats harbour fleas in small numbers, but there is no evidence that they ever attack man.

There can be little doubt that the bite of a larval mite is responsible for the entry of infection. The progress of an ordinary bite is as follows: it does not give rise to any symptoms for the first six to twelve hours; then a papule, three to six millimetres across, appears; it is topped by a tiny blister and surrounded by a red areola, and it itches intolerably. It is rare to find the larva once the blister has formed—it either drops off when engorged, or is rubbed off immediately the itching develops. On being scratched, the blister is torn open and becomes infected easily. Such sores rapidly break down to small, indolent ulcers, very stubborn and inclined to spread. If the bite of a larval mite is the origin of the eschar, then such a bite must follow a different course. It must have had only a slight or else a transient itchiness, otherwise it would have been scratched and become secondarily infected; whereas the outstanding features of an eschar are that it is often unnoticed by the patient for days, and that there is never any history of previous ulceration at its site. The probable explanation is that early invasion of the bite by the virus anæsthetizes it, as an early stage in the process of necrosis. In a few cases a small dusky area has been noticed as early as five days before the onset of the disease, at the site later occupied by an eschar. In one case, by the time the disease developed there was some subcutaneous softening in the centre of an area of this kind, and the hard black slough did not develop until a few days later.

The New Guinea Mites.[22][23]

When I came to investigate those larvæ of the family Trombidiidæ which might be found in New Guinea, I discovered no less than 18 species, of which 16 were new; and I had to work them all out before I could proceed. In addition there are two species known from Dutch New Guinea, included here for the sake of completeness. In the following list the hosts of the various species are shown by their vernacular names; full details are available in the papers referred to at the head of this section; certain further details are in other papers referred to opposite the various mites concerned. The following are the known New Guinea mites, with the hosts on which they have been found:

1. *Trombicula minor* Berlese, 1905.
   Syn.: *Trombicula hirsti* var. *buloloensis* Gunther, 1939.[24]
   Principal hosts: Bandicoot, bush pig, bush fowl, bush turkey, cassowary, ground pigeon. Casual hosts: Rail, swamp hen, man.
2. *Trombicula rioi* Gunther, 1939.
   Casual host: Bush fowl.
3. *Trombicula vanderghinstei* Gunther, 1940.
   Principal host: Rat.
4. *Trombicula wichmanni* (Oudemans) 1905.[25]
   Principal host: Goura pigeon. (Dutch New Guinea.)
5. *Schöngastia jamesi* Gunther, 1939.
   Casual hosts: Bandicoot, bush fowl.
6. *Schöngastia blestowei* Gunther, 1939.
   Principal host: Bush fowl. Casual host: Man.
7. *Schöngastia taylori* Gunther, 1940.
   Principal host: Scrub wallaby.
8. *Schöngastia vandersandei* (Oudemans) 1905.[26]
   Casual host: Man. (Dutch New Guinea.)
9. *Neoschöngastia impar* Gunther, 1939.
   Principal hosts: Five species of rats, two of bandicoots.
10. *Neoschöngastia lorius* Gunther, 1939.
    Principal host: Parrot.
11. *Neoschöngastia edwardsi* Gunther, 1939.
    Casual hosts: Bush fowl, bandicoot.
12. *Neoschöngastia womersleyi* Gunther, 1940.
    Principal host: Scrub wallaby.
13. *Neoschöngastia foliata* Gunther, 1939.
    Principal host: Scrub wallaby.
14. *Paraschöngastia yeomansi* (Gunther) 1939.
    Principal host: Bush fowl.
15. *Paraschöngastia backhousei* (Gunther) 1939.
    Casual host: Bush fowl.
16. *Paraschöngastia retrocincta* (Gunther) 1939.
    Principal host: Bush fowl.
17. *Paraschöngastia dubia* (Gunther) 1939.
    Casual host: Bush fowl.
18. *Guntheria bipygalis* (Gunther) 1939.[20]
    Principal hosts: Six species of rats. Casual hosts: Two species of bandicoot, one species of rat.
19. *Walchia morobensis* Gunther, 1939.
    Principal hosts: Two species of rats.
20. *Leeuwenhoekia australiensis* Hirst, 1925.[27]
    Principal hosts: Bush turkey, five other species of birds. Casual hosts: Three species of birds.

Trombicula Minor Berlese, 1905, as the Probable Vector.

When a likely vector is being sought attention should first be directed to any mite which has as its principal host a rodent or similar animal, and which at the same time numbers man among its casual hosts. The latter condition limits the choice to *Trombicula minor* (of which I have taken 70 specimens from 11 men), *Schöngastia blestowei* (55 specimens from 9 men), and *Leeuwenhoekia australiensis* (of which I have taken no specimens from man in New Guinea, but which is reported to be a common parasite of man in Australia). The last two do not fulfil the first condition, since they have no other hosts than birds; but *Trombicula minor* has been found on the bandicoot *Echymipera cockerelli* Ramsay, 1877. Therefore, if this way of approaching the problem is a feasible one, then in the light of our present knowledge *Trombicula minor* is the only possible vector.

There is a general argument which is worthy of consideration. In most other diseases we have examples of the remarkable way in which the role of vector or of host is confined strictly to one genus. There are, for example, the mosquitoes, with their association of malaria with the genus *Anopheles*, yellow fever and dengue fever with the genus *Stegomyia*, and filariasis with the genus *Culex*. Now, *Trombicula akamushi* has long been incriminated as the vector of *tsutsugamushibyo* in Japan; as far back as 1927, *Trombicula minor* (*Trombicula hirsti*) was indicated by Sambon as the probable vector of "Mossman fever" in North Queensland;[28] and Sumatran mite fever[29] and Malayan scrub typhus[30] are carried by *Trombicula deliensis*. It is therefore quite logical to look within the genus *Trombicula* for the vector in New Guinea. Of the three local members of this genus (the Dutch species does not come within the scope of the present discussion), only *Trombicula minor* meets our requirements; *Trombicula rioi* does not attack man, and has no host other than a bird; *Trombicula vanderghinstei* certainly has a rat as its principal host, but so far has been found in only one limited locality, where endemic typhus does not occur, and it has not been taken on man.

Elsewhere in the world, the species which are known to attack man are limited to three genera: *Trombicula*, *Schöngastia*, and *Leeuwenhoekia*. If we confine our search within these genera, only seven mites are eligible. Three of these have no other hosts than birds; of those that remain, *Trombicula vanderghinstei* has already been

eliminated in favour of *Trombicula minor;* and *Schöngastia jamesi* and *Schöngastia taylori*, although they have marsupial hosts, have not so far been taken on man.

Altogether, ten species of mites occur on rats, bandicoots and wallabies. It is possible that one or more of these may be in the habit of attacking man occasionally, even though so far none has been observed to do so. In that case they would come under suspicion as possible vectors. *Trombicula minor, Neoschöngastia edwardsi,* and *Schöngastia jamesi* occur on the bandicoot. Only one specimen of each of the last two has been taken from all the bandicoots so far examined, whereas *Trombicula minor* is particularly numerous on this host, which implies that it is the most likely vector among these three.

Five species of rats and two species of bandicoots harbour *Neoschöngastia impar*, all in the role of principal host. This species could be a vector. *Guntheria bipygalis* has the same five species of rats as its principal hosts, and the two species of bandicoots as casual hosts. It would appear to be much more intimately associated with its rodent hosts than are the other members of the family, since its ova are found cemented to their abdominal hairs—a phenomenon which suggests a life cycle confined almost entirely to the nests of its hosts. I believe that this would hardly permit of its being considered a likely vector.

Trombicula vanderghinstei occurs on one species of rat, which has a very limited location, but there is nothing to bar it as a possible vector. *Walchia morobensis* has extremely narrow limitations; it is found only on and around the edges of the nostrils of two species of *Rattus*. Because it shows this strict selectivity I regard it as a most unlikely vector. Of the three species which have been found on the wallaby, none can be excluded, unless *Neoschöngastia womersleyi* and *Neoschöngastia foliata*, together with *Neoschöngastia impar*, are ruled out because members of this genus do not attack man anywhere in the world.

To sum up, the potential vectors are *Trombicula minor, Trombicula vanderghinstei, Schöngastia blestowei, Schöngastia jamesi* and *Schöngastia taylori*. On the available evidence, *Trombicula minor* seems to be the only possible choice as the vector from the bandicoot to man; *Neoschöngastia impar* seems easily to fit into the picture as the vector between the rats and the bandicoot. This view can be held only so long as there is no proof that none of the other species attacks man. It has not been possible to arrange experiments at Bulolo to confirm these findings; and since the infection does not remain alive outside living cells, emulsions of suspected mites cannot be transported to any place where these experiments could be carried out. I have tested larvæ and found that they will remain alive for at least ten days in a small sealed tube provided a little moisture is present; such a tube could be safely packed so that there would be no risk of the larvæ escaping alive if it were broken; but so far I have not been able to make any arrangements to have any work done in Australia on these lines. Hence the question must be decided on epidemiological lines alone, for the present.

Since *Trombicula minor* infests all the common ground birds as well as the bandicoot, it will be seen that only those individuals which come to man from the bandicoot (a small proportion of the available total) would be infectious. This would be consistent with the fact that while many are bitten by mites, only few develop the disease.

The Reservoir of the Disease.

The choice of animals which could be regarded as likely reservoirs of the disease is obviously limited to those which harbour larval mites. Naturally, all these animals probably suffer from the disease; but the effective reservoir (the one from which man directly acquires his infection) can only be the animal which harbours *Trombicula minor*. This is the bandicoot *Echymipera cockerelli* Ramsay, 1877. Although bandicoots are not rodents (they are small marsupials, of the family Peramelidæ, peculiar to Australia and the adjacent islands), recent studies by a group of workers on "Q" fever, which is a rickettsial disease occurring in North Queensland, have shown that the bandicoot *Isoodon torosus* Ramsay, 1877, is susceptible to the disease, and is involved in the cycle of its occurrence in the bush,[32] while Mathew, working on endemic typhus in the same region, has found that the serum of two bandicoots, *Isoodon macrourus* Gould, 1842, and *Perameles nasuta* Geoffroy, 1804, commonly agglutinates *Bacillus proteus* Kingsbury.[29] Other marsupials, *Didelphis aurita* and *Didelphis paraguayensis*, have been proved by Travassos[33] to be susceptible to Sao Paulo typhus virus and to harbour it in their natural state. Brigham has done similar work on *Didelphis virginiana*.[34] Although these findings are concerned with the X19 subgroup, the fact that a rickettsial infection can affect these opossums is significant; there is every possibility that wallabies also could be involved in the cycle of rickettsial diseases.

I have examined direct smears from the livers and spleens of six bandicoots and 20 rats, stained by Giemsa's method, without finding any rickettsial bodies; but I have reason to believe that my staining technique was faulty. It is possible that more certain results could be obtained by using the technique devised by Burnet and Freeman.[35]

Endemic Typhus in Dutch New Guinea and Papua.

Although de Rook, in his report on the state of health (*Gezondheidstoestand*) in Dutch New Guinea, stated that endemic typhus did not occur there,[18] I saw a fatal case in Wewak in which the disease had undoubtedly been contracted within a very few miles of the border of Dutch New Guinea. De Rook also mentions that irritation due to red mites (*thrombidien*) is common. The only mites so far described from Dutch New Guinea are *Schöngastia vandersandei*, which has man as its casual host, and *Trombicula wichmanni*, which has the goura pigeon as its principal host (but which attacks man in North Celebes).

Although there is nothing but an unconfirmed suspicion that certain fatal cases of an undefined fever among Papuan natives may have been endemic typhus, what has been said of natives of the mandated territory does not apply to Papuans. These are ethnologically a different race; and while our natives only rarely complain of mite bites, the Papuans suffer severely. Mites abound on the Papuan mainland, except in the dry belt around Port Moresby. They have not been investigated; but Lupson in a personal communication says that "scrub itch" in the Delta Division is caused by a mite resembling *Trombicula hirsti* (*Trombicula minor*).

Cases of endemic typhus have already been reported at Ramu, close to the Papuan border, and at Green River, almost on the border of Dutch New Guinea. All the cases in New Guinea have occurred in that portion of the island limited by the great mountain ranges which separate the rivers flowing north and east through the Territory of New Guinea from those flowing south through Papua and west through Dutch New Guinea. It is likely that the intense cold and heavy rainfall prevailing at the upper levels of these high ranges would prove an effective barrier to the local migration of animals which harbour mites or act as reservoirs of the disease, since these are all small rodents, or marsupials, or ground birds, acclimatized to tropical conditions. Nevertheless, even if endemic typhus should be thus limited to the mandated territory by the natural boundaries of the interior, there is a possibility that it may spread along the coastal districts into the neighbouring territories, now that the country is being opened up. There is apparently no dearth of potential vectors in either territory, and the report of Brigham and Dyer on the spread of endemic typhus in the south-east of the United States of America[36] offers evidence that such a spread is not impossible.

Prophylaxis.

Deliberate methods for making the skin distasteful to mites have been tried, usually as a means of preventing the itching of ordinary bites. Susceptible persons have painted themselves with permanganate of potash solution, olive oil, dripping, castor oil or kerosene, with various degrees of success. The dusting of flowers of sulphur into the socks has been recommended; but there is a serious risk of sulphur dermatitis if this is kept up for any length

of time. I have been strongly advised to anoint myself from the waist down with a mixture of equal parts of kerosene and friction grease, by one sufferer who considered this better than the irritation of the bites. The method does not appeal to me. In fact, I know of no useful preparation which will render the skin distasteful to mites.

There are also various measures in vogue for dealing with the itching bites. Tearing off the top and rubbing in permanganate of potash crystals, and cauterization with a red hot wire or a lighted cigarette, are among the more drastic of these. Doubtless such treatment would destroy any virus introduced into a bite, but, as has already been pointed out, an infected bite probably does not itch, so that the chances of finding one in order to treat it are few. It has also been pointed out that once the disease has manifested itself, excision of the eschar makes no difference. This was only to be expected, but it is more reasonable to suppose that excision while the infection is still localized may have better results. Since it is now known that the eschar may be present in a recognizable form as early as five days before the onset of general symptoms, prophylactic excision is possible, and should be well worth a trial.

Although the development of vaccines for protection against the louse-borne and flea-borne members of the typhus group of fevers is meeting with success, and prophylaxis against Rocky Mountain spotted fever is an established measure, there seems to have been no advance in this direction as far as the mite-borne diseases are concerned. Kawamura and his co-workers have found that *tsutsugamushibyo* in the Pescadores is "identical with that met with in Japan, but the mortality rate is much lower".[37] While experimenting with this mild form as a substitute for malaria in the treatment of nervous syphilis, they discovered that after eight days it conferred immunity against the more potent Japanese variety.[38] Whether it would do so after an interval of months has not yet been investigated. In Malaya it has been shown that although the Proteus reaction may persist *in vitro*, the therapeutic value of preserved serum deteriorates rapidly; thus the fact that in the Japanese form of the disease the Proteus reaction persists for years *in vivo* offers no real proof that the anti-rickettsial reaction persists too. Manson-Bahr[39] mentions that one attack of *tsutsugamushibyo* does not confer immunity. All things considered, it is doubtful whether any useful vaccine for the mite-borne group can be devised.

Theoretically, fresh convalescent serum of high titre should confer some passive immunity, but the effect is likely to be too evanescent for practical purposes.

The following are suggested measures which aim at minimizing the risks of contracting the disease.

1. The systematic trapping and burning of rats and bandicoots around camp sites, and proper disposal of rubbish likely to attract them. Poison baits should not be laid, since the mites would only leave the carcasses and seek new hosts immediately; this might increase the risk of being bitten.
2. The restriction of activity, wherever possible, to pathways and clearings which have been burnt off. Paths should be cut at least four feet wide, and the grass and brush should be burnt where it lies.
3. The taking of a bath immediately on coming in from work in the bush, particular attention being paid to the sites favoured by the mites, with the use of a soft nail-brush and a thick lather of soap.
4. The watching of these sites for the earliest appearance of an eschar, so that it can be identified and excised before the onset of general symptoms, in the hope of aborting the threatened attack.
5. The instruction of all bush workers by the distribution of circulars embodying these points, with sufficient explanation to make them intelligible to laymen.

Endemic Typhus of New Guinea in Relation to the Other Members of the XK Subgroup.

Kawamura has described three forms of *tsutsugamushibyo*;[40] that from Japan is the most severe, it has the highest mortality rate, and gives the highest reactions against *Bacillus proteus* Kingsbury (up to 1/25,000); the other forms are much milder and have a very low mortality rate; that from the Pescadores gives a lower range of titres against the Kingsbury strain, while the Formosan form is the lowest of all. An eschar is constantly present in Japan, but is often absent in the other regions. The Proteus reaction in the Japanese variety may persist for several years after an attack. Cross immunity has been demonstrated between these varieties.

O'Connor[41] has emphasized the close relationship between Malayan scrub typhus and *tsutsugamushibyo*, except that in the former no eschar is present. Scrub typhus has a mortality rate of 4·7%, the rash appears on the fifth or sixth day, and the agglutination reaction does not appear until after the fever has subsided. Lewthwaite and Savoor describe Malayan scrub typhus and the local Malayan form of *tsutsugamushibyo* as identical except for the absence or presence of an eschar;[42] complete cross immunity exists between them;[43] they consider that they are one and the same disease, and that the name "scrub typhus" should be dropped.[44] Nevertheless they describe definite differences between the two types in the extent of the local lymphadenitis: when there is no eschar, the lymphadenitis is severe, while if an eschar is present it is mild. This certainly points to the existence of some factor which has not yet been discovered; the probability is that the vector or vectors are concerned in some way.

Kouwenaar and Wolff[10] state that an eschar invariably appears in Sumatran mite fever. The mortality rate is 40% in Europeans, but only 5% among the Javanese. Clinically it cannot be differentiated from *tsutsugamushibyo*; but the virus produces only mild effects in monkeys, whereas it affects guinea-pigs severely; this is the reverse of what occurs in *tsutsugamushibyo* and in Malayan scrub typhus. They also state[45] that Sumatran scrub typhus has no eschar, but is otherwise identical with mite fever; neither of these conditions possesses a cross immunity against *tsutsugamushibyo*.

These are the main varieties of the disease. It has also been reported in one form or another from the Simla Hills,[46] Cochin China,[47][48][49] North Queensland,[50][51] India generally,[52] Indo-China,[53][54][55] Borneo,[56] Burma[57] and Ceylon;[58] but these forms have not been investigated thoroughly enough to enable them to be classified.

Broadly speaking, the differences between all these groups fall into three categories: differences between the severity of the local lesions, the severity of the general reactions, and the selective action of the virus on laboratory animals. None of these phenomena depend on essential variations in the nature of the infecting organism, but they could all be accounted for by modifications in its action produced by local variations in vectors and reservoir animals. Just as vaccinia, although modified by passage through cows, is yet essentially the same disease as variola, so the mite-borne fevers, wherever they occur, may be regarded as grades or facets of the one essential disease, modified by such factors as the vector-efficiency of local species of mites and the biological modifications which various animals acting as reservoirs may have on its potency or selectivity. The fact that, in Japan, *Trombicula akamushi* transmits *tsutsugamushibyo* directly to man from the field vole *Microtus montebelloi*, may account for the higher virulence of this form of the disease as compared with that found in New Guinea, where apparently *Trombicula minor* obtains its infection from the bandicoot; had there been in New Guinea a direct mite vector from rats to man (with consequent elimination of the intervening passage through the bandicoot), the disease might conceivably have shown a higher virulence. It is not impossible (indeed, it is almost inevitable) that, during the carry-over of a rickettsial infection in mites from one blood-sucking larval generation to the next, a developmental cycle takes place, analogous to that of the malarial parasite in the mosquito; the presence or absence of an eschar may be determined by the way in which the virus is modified by different species of mites during this developmental cycle; on the other hand, it might even be determined by the quality of the salivary secretion and the efficiency of the piercing, injecting and sucking mechanism of the particular vector

concerned. Purely hypothetical as these suggestions are, they nevertheless indicate what I believe to be the best line of thought to be followed in the consideration of the problems of the mite-borne diseases.

My conception of these diseases is that, starting originally from a single focus (perhaps Malaya, perhaps Japan), there has been a gradual spread until they have now reached their present locations throughout the Far East. The geographical distribution of the known species of mites is interesting; Europe has a trombidiid fauna all its own, and so has America; neither of these groups is represented in the Far East, which has about one hundred known species, many overlapping several regions (*Trombicula minor*, for instance, occurs in Malaya, the Dutch East Indies, Formosa, New Guinea, and Australia, with only negligible local variations). This self-contained group of Asian and Australasian mites occupies exactly the same territory as the known mite-borne diseases of the XK subgroup of Felix. (Curiously enough, there has been no record of any of these diseases from China, nor have any Chinese mites been described.)

Exactly where the New Guinea variety fits into the general plan is hard to determine. With its lower titre range and impermanent Proteus reaction, it obviously differs from the Japanese variety; it invariably has an eschar, and so is different from those of Formosa and the Pescadores. The absence of an eschar in both Malayan and Sumatran scrub typhus sets it apart from these also. Sumatran mite fever has a mortality rate of 40% in Europeans, which is more than twice that of the New Guinea variety. It has not been possible to assess the relative effects of the latter on monkeys and guinea-pigs.

The New Guinea variety apparently has an individual place; like all the others, its claims to individuality are meagre and indefinite—too indefinite for practical purposes. If the broad conception outlined above is accepted, then no exact, systematic grading of any of these diseases is possible, since the features of each are determined arbitrarily by the local reservoir animals and vectors, and the most that can be said is that the New Guinea variety occupies a place intermediate between the Formosan and Japanese forms; alternatively, it can be grouped with Sumatran mite fever, but below it in the scale of virulence.

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SOME OBSERVATIONS ON ENDEMIC TYPHUS IN SOUTH AUSTRALIA.

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IN South Australia, a condition with all the clinical features of typhus fever was first described by Hone.[1][2][3] The disease is endemic in this State, though the number of cases each year is small. According to the Report of the Federal Health Council of Australia,[4] 120 cases were detected from 1921 to the end of 1929. In 1932, notification of the disease became compulsory; the number of cases since recorded is given in Table I.

TABLE I.
Number of Cases of Typhus Notified in South Australia since 1932.

Year.	Number of Cases.	Number of Deaths.
1932	4	1
1933	8	—
1934	8	—
1935	14	1
1936	13	3
1937	6	—
1938	7	—
1939	4	—
Totals ..	64	5

Thus, an average of eight cases has been notified each year for the last eight years. It is probable, however, that many other cases occur and escape recognition, as they are not clinically characteristic. The Weil-Felix test with Proteus OX19 is useful in diagnosis, and the response is generally positive in cases in which typical symptoms are present. However, some patients suffering from pyrexia of uncertain origin have symptoms and rash almost indistinguishable from those of typhus, yet the blood fails to give a positive agglutination reaction with either Proteus OX19 or Proteus OXK. Another type of fever has been referred to as "hills typhus" by practitioners in the Mount Lofty Ranges; in this also the Weil-Felix test fails to produce a reaction.

The diagnostic significance of a positive agglutination reaction with Proteus OX19 obviously depends on the frequency with which agglutinins for this organism are met with in serum from normal persons and from patients suffering from other types of pyrexia. At the same time, it must be remembered that a positive reaction may be due to a previous attack of typhus, although Felix[5] points out that the reaction persists for not longer than five months after recovery. Most of our results are in conformity with this belief.

The present work records an investigation of the presence of agglutinins for Proteus OX19 in blood sent in for Wassermann tests, in the blood of patients suffering from various pyrexial conditions, and in that of persons recovered from typhus fever. These results may assist in the interpretation of positive agglutination reactions with Proteus OX19. At the same time, tests were made with Proteus OXK and a local strain, Proteus O Hill, as well as with H antigens of all the Proteus strains.

In an endeavour to discover a natural reservoir of typhus, agglutination tests with all the Proteus antigens were performed on the serum of wild rats from various districts. The brains of the rats were sectioned and examined histologically for typhus nodules. Attempts were also made to recover from rats and from human patients the virus of endemic typhus not yet isolated in South Australia.

Methods for the Agglutination Tests.

Antigens.

The H antigens consisted of formolized broth cultures of actively motile strains of Proteus X19, Proteus XK and Proteus Hill. No standard H suspensions of Proteus were available for standardization of these antigens, but all were tested for agglutinability with antisera prepared in the rabbit against Proteus X19 and Proteus XK. The HX19 and HXK antigens were agglutinated to the same titre, while H Hill showed only partial agglutination up to half-titre.

The O antigens were prepared from smooth cultures by the method of Bien.[6] Again, no standard suspensions were available for comparison; but the OX19 antigen was compared with one used in the institute for routine tests and also with another supplied by the Commonwealth Serum Laboratories. The routine antigen was twice as agglutinable as either of the others, both of which gave the same titre when tested out with rabbit antiserum. An agglutinability factor of 0·5 was therefore assigned to the OX19 antigen used in this study. The OXK antigen was compared with a suspension kindly supplied by Dr. W. G. Heaslip. This antigen agglutinated to twice the titre of our antigen with rabbit antiserum, and with human serum from patients suffering from typhus. Therefore, our suspension was also given an agglutinability factor of 0·5. The O Hill antigen was not agglutinated to any significant titre with either Proteus X19 or Proteus XK serum and was not standardized. The strain Proteus Hill from which the antigens were made was isolated locally from a gall-bladder.

Serum.

None of the specimens of serum used in these tests had been inactivated, and all were tested within one to six days of collection.

Technique of Agglutination Tests.

Twofold dilutions of serum were made in saline solution from 1/5 to 1/40. An equal volume of bacterial suspension was added to each tube, the final range of dilutions being from 1/10 to 1/80. Further dilutions were made and tested when necessary. The tubes were incubated overnight in a water bath at 55° C. and the results were read with a lamp over a dark background. The titres recorded are those at which standard or complete agglutination was present. In the tests with the O antigens all titres are given after adjustment for agglutinability of the suspension; for example, if our Proteus OX19 antigen gave a titre of 1/20 with a certain serum, then the recorded titre would be 1/40 because the agglutinability factor of the antigen was 0·5.

Results.

Serum Sent in for the Wassermann Test.

The tests performed on specimens of serum sent for the Wassermann test were intended to give some idea of the frequency of occurrence of "normal" agglutinins for the various Proteus strains. There were 161 specimens, and of these 104 gave no reaction at a dilution of 1/20 with the H or O antigen of any Proteus strain. The results with the remaining specimens are given in Table II.

TABLE II.

Results of Testing 161 Specimens of Human Serum with various Proteus Antigens.

Proteus Antigen.	Number of Specimens of Serum Giving a Titre of:				
	1/20	1/40	1/80	1/160	1/320
HX19	1	—	—	—	—
OX19	8	1	—	—	—
HXK	5	2	1	—	—
OXK	4	2	—	—	—
H Hill	27	17	6	3	1
O Hill ..	5	1	—	—	—

From Table II it can be seen that agglutinins for the H antigen of the local strain Proteus Hill were met with quite frequently in the lower dilutions, while three specimens of serum yielded positive results at a dilution of 1/160 and one at 1/320. With serum diluted to more than 1/40, agglutination of the other antigens was rare. Even at 1/40 very few specimens of serum gave positive results. At 1/20, however, the numbers were larger, and it is interesting that at this dilution all the antigens have given a positive result with at least one specimen of serum. Since eight out of 161 specimens of serum gave a positive result at 1/20 with Proteus OX19, agglutination to this titre must be regarded with caution in the diagnosis of typhus fever. A titre of 1/40 would be more significant, as "normal" agglutinins were detected in only one specimen of serum at this dilution. Much the same consideration would apply in the case of Proteus OXK if this antigen was used in diagnostic tests in this community.

Serum from Patients Suffering from Pyrexia.

The blood serum from 182 patients suffering from pyrexia was tested for agglutination of Proteus OX19. The disorders included typhus as well as typhoid fever and other pyrexial conditions; it was to be expected, therefore, that there would be more positive results with Proteus OX19 than in the case of serum sent for the Wassermann test. Actually 160 specimens of serum gave no agglutination with Proteus OX19 at a dilution of 1/20. The remaining 22 samples gave positive reactions to varying titres. Of the 22 cases from which these specimens were taken, six were diagnosed clinically as typhus fever. In two of these cases the titre was 1/160, while in the other four cases the titres were over 1/1,000. Thus, if we deduct the number of typhus cases (6) from the total number tested (182), there remain 16 out of 176 cases of pyrexia in which agglutinins for Proteus OX19 were present in the blood. Of these 16 cases, one showed agglutination at 1/80, six at 1/40 and nine at 1/20. It appears, therefore, that agglutinins for Proteus OX19 are rarely found at a titre higher than 1/40 in fevers other than typhus fever.

Serum from Persons Recovered from Typhus.

Blood was collected from fourteen persons who had suffered from typhus fever not less than twenty months earlier. Agglutination tests were performed with H and O antigens of Proteus X19, XK and Hill. There were no agglutinins in a dilution of 1/20 for any of the O antigens. Two specimens of serum agglutinated Proteus HX19, one at 1/40 and one at 1/20; two specimens of serum agglutinated Proteus HXK at 1/20; and the local strain Proteus H Hill was agglutinated by nine specimens—two at 1/80, two at 1/40, four at 1/20, and one at 1/10. These results are very like those found with the specimens of serum for Wassermann testing; they show that usually the agglutinins produced by an attack of typhus fever are not evident after twenty months, when the serum behaves towards strains of Proteus in much the same manner as that from persons who have not suffered infection.

On one occasion, blood collected from a person who had suffered from typhus nine months previously gave a positive agglutination reaction with Proteus OX19 to a titre of 1/640, and agglutinins could still be detected up to two years after recovery. In six persons who had suffered from typhus and whose blood still contained agglutinins for Proteus OX19, no rise in titre was observed to follow an attack of influenza (five cases) or of pyelitis (one case).

Serum from Rats.

Blood was collected from 33 rats caught in Adelaide and suburbs. The results of agglutination tests with the various Proteus antigens are given in Table III.

TABLE III.

Results of Testing Thirty-three Specimens of Serum from Rats with various Proteus Antigens.

Proteus Antigen.	Number of Specimens of Serum Giving a Titre of:				
	1/10.	1/20.	1/40.	1/80.	1/160.
HX19	3	3	2	2	1
OX19	1	—	—	—	—
HXK	2	2	1	1	1
OXK	2	—	—	—	—
H Hill	—	—	—	—	—
O Hill ..	—	—	—	—	—

The results in Table III show that H agglutinins for Proteus X19 and XK are present in the serum of some rats in a dilution as high as 1/160, while O agglutinins for these organisms are less frequently present, and then only in low concentration. The local strain, Proteus Hill, was not agglutinated at all by any of the serum from rats. This is in marked contrast to the results with human serum given in Table II, in which agglutination of Proteus H Hill was common.

Histological Examination of Brains from Rats.

The brains from the 33 rats referred to above were sectioned, stained and examined microscopically for typhus nodules. In none was there conclusive evidence of the presence of the typhus nodules described by authors elsewhere (see Lillie, Dyer and Topping[7]).

Attempts to Recover the Virus of Typhus.

From each rat brain examined histologically, a portion was retained, emulsified in saline solution and injected intraperitoneally into guinea-pigs. No apparent effect was produced in these animals.

Numerous fleas, mainly *Xenopsylla cheopis*, were collected from a number of rats. A suspension was made by trituration in normal saline solution and injected intraperitoneally into guinea-pigs, mice and rabbits. In no instance was any definite reaction produced. The brains of these rats were similarly treated, with similar negative results.

At various times during the illness, blood was collected from ten patients suffering from endemic typhus. Whenever possible, the first specimen was taken before the appearance of the rash, the second specimen on the

appearance of the rash, and the last specimen later in the illness. In every case the blood was defibrinated and injected intraperitoneally into guinea-pigs; some specimens were also injected into mice and rabbits. No definite reaction was noted in any of the animals, and no Rickettsiæ were detected in smears from the *tunica vaginalis* or spleen. Some of the animals used in the later tests were partly shaved and were kept cold by being sprinkled with water and placed in a draught. These animals also showed no definite reaction.

Blood from a patient suffering from so-called "hills typhus" was inoculated intraperitoneally into two guinea-pigs. One of these animals died eighteen days after injection; a post-mortem examination revealed a hæmorrhagic peritonitis, patchy bronchopneumonia and an apparently normal spleen. The second guinea-pig died two days later, and showed similar post-mortem appearances. Material from each of these guinea-pigs was inoculated into guinea-pigs, rabbits and mice; some of these died and showed lesions closely resembling those of the first two animals. Most of the animals had a subnormal temperature commencing a few days before death. These findings appeared fairly uniformly throughout successive passages during the next two months. The inoculum in some instances was filtered through a Chamberland L candle. Attempt at cultures from the filtrate yielded no growth, but the filtrate retained its effect on guinea-pigs until after ten weeks the infective factor was lost. A few of the animals showed punctate hæmorrhages in enlarged suprarenal glands, but the most striking feature was the uniformity of the pathological condition in the lungs and peritoneal cavity. Rickettsiæ were not found.

Some Clinical Observations.

In one case of typhus in which the serum agglutinated Proteus OX19 to a titre of 1/2,560, a possible primary sore occurred on the lower part of the abdomen. Though the primary sore is common in "coastal" or "tropical typhus" in Queensland and New Guinea, it has not been recorded in South Australia.

The patient, a ham-shop proprietor, was a short, very fat man, weighing about 22 stone. He remembered being bitten, he thought by a flea, on the lower portion of the abdomen about ten days before his illness. This commenced with the usual severe headache and accompanying symptoms. When he was examined he had been ill for two days and had been delirious and getting out of bed. At this time the sore was a small, angry, red papule about two to three millimetres in diameter, surrounded by a red hyperæmic area with indistinct margins extending to an average diameter of about five centimetres. During subsequent days the papule broke down and spread until it left an ulcer of about 1·5 centimetres in diameter, with a red, granulomatous, indurated base. The patient complained of pain in the groins, but, owing to fat, it was not possible to feel any enlarged glands. His daughter contracted typhus at about the same time, but did not exhibit a sore.

In each of these cases, and in one other, very considerable relief and rapid fall in temperature occurred within the usual twelve days following the administration of a simple aspirin, phenacetin and caffeine mixture.

Among persons recovered from typhus, even as long ago as fourteen years, a common complaint was the persistence of severe headache. Most patients stated that they had not suffered from this complaint before contracting typhus. Some persons also complained of inability to concentrate; others complained of "weakness of the heart" ever since their illness. In classical typhus, the occurrence of a gliosis about the arteriolar necrotic patches in the cerebral vessels might explain the persistence of headache.

Discussion.

Out of 351 specimens of serum, of which 161 were sent in for the Wassermann test, 176 were collected from patients suffering from pyrexia other than typhus fever, and 14 were taken from persons recovered from typhus, only one specimen agglutinated Proteus OX19 at a dilution of 1/80, and none agglutinated at a higher dilution. Thus, it appears that in South Australia agglutinins for Proteus OX19 are rarely found at a titre higher than 1/40 in the blood serum of persons not suffering from typhus fever. In the interpretation, therefore, of a positive reaction to the Weil-Felix test, agglutination at a dilution of 1/80 would be suggestive, and at a higher dilution could be regarded as diagnostic of typhus fever, provided that the patient had not recently recovered from the disease.

In the United States of America, Savoor, Castaneda and Zinsser[8] obtained a greater number of positive reactions at 1/80 and 1/60 than were found here. Out of 596 specimens of serum from various sources they found 25 to give positive reactions at 1/80 and four at 1/160. However, it is possible that some of these patients had recovered recently from typhus fever or were suffering from a mild form of the disease; this would account for the larger number of positive results. Pasricha, Bannerjee and Lal[9] also record among natives of India more positive reactions at higher titres than were encountered here. The patients were suffering from various diseases, but none had typhus fever or gave a history of recent typhus infection. Out of 280 specimens of serum tested with Proteus OX19, 23·2% gave a positive reaction at 1/50 and 1·4% at 1/100.

The origin of these "normal" agglutinins for Proteus OX19 is debatable. It seems unlikely that they are produced by the specific stimulus of typhus infection, as the positive response to the Weil-Felix test disappears soon after recovery. They may be produced by contact with Proteus X19 or with other organisms possessing similar somatic antigens. If this mechanism is responsible, our results suggest that in South Australia contact with such organisms is rare.

Tests with the other Proteus antigens showed that agglutinins for Proteus OXK, HXK and O Hill also occurred infrequently. With Proteus H Hill, however, numerous positive reactions were obtained at a low titre, and some specimens of serum gave positive results at a titre of 1/160 or 1/320. As Proteus Hill is a local strain, these agglutinins most probably arose from low-grade or secondary infections with this or a related organism. The presence of these agglutinins was unrelated to the age of the patient.

In other countries where rats have been incriminated as the reservoir of typhus infection, many of these animals gave positive reactions to the Weil-Felix test, and no great difficulty was encountered in demonstrating the presence of the typhus Rickettsiæ (see Kligler and Comaroff,[10] Lewthwaite and Savoor[11]). In all our tests with rats we could find no evidence of typhus infection in these animals; this suggested that endemic typhus in South Australia might have its reservoir in some other animal. It must be mentioned, however, that none of our rats came from a district in which a case of typhus had recently occurred.

Summary.

Agglutination tests with Proteus OX19 were performed with serum from 351 persons not suffering from typhus fever. The highest titre recorded was 1/80, and was found in only one specimen of serum; seven specimens gave a titre of 1/40 and seventeen a titre of 1/20.

In tests with H and O antigens of Proteus XK and Hill on 161 specimens of serum sent in for the Wassermann test, it was found that agglutinins for Proteus OXK, O Hill and HXK were rarely found at a dilution greater than 1/20. Agglutinins for Proteus H Hill, a local strain, were encountered more frequently; one specimen of serum had a titre of 1/320, three specimens had a titre of 1/160 and six had a titre of 1/80.

The blood of 33 wild rats was tested with all our Proteus antigens. One specimen of serum gave a titre of 1/10 with Proteus OX19 and the others gave negative results. Two specimens of serum agglutinated Proteus OXK at 1/10 and several specimens agglutinated the H antigens of both Proteus X19 and Proteus XK at titres of from 1/10 to 1/160. No serum agglutinated the Proteus Hill antigens.

No typhus nodules or Rickettsiæ could be detected in the brains of these or other rats. Typhus was not produced in guinea-pigs, mice or rabbits inoculated with suspensions of fleas collected from rats, or with defibrinated blood taken at various stages of human endemic typhus.

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Reports of Cases.

PAUSE IN THE GROWTH OF THE FŒTUS, WITH PROLONGED PREGNANCY.

By MARY C. DE GARIS.

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Clinical Record.

A MARRIED woman, aged about twenty-one years, attended the antenatal clinic for the first time on October 7, 1937. She had one child, aged eighteen months, and she had had no miscarriages. At the time of her first attendance at the clinic the uterus was about the size of a four months' pregnancy; the last menstrual period had taken place from June 8 to June 15, and the date of her confinement was calculated as March 15, 1938. The menstrual periods had been painless since her first delivery, although somewhat irregular; they usually occurred every four weeks and lasted for one week. The patient complained of much morning sickness and of giddiness. She was receiving "sustenance", and her diet was bad; no milk, no fruit and no green vegetables were taken. She had much dental caries and suffered from toothache. Arrangements for extra food were made. The patient attended at the clinic eleven times during her pregnancy.

On December 2, 1937, the uterus was the size of a four or four and a half months' pregnancy, and no fœtal movements had been felt. It was thought that the fœtus was probably dead; however, it was decided merely to keep the patient under observation.

On January 13, 1938, the uterus was at umbilical level, a uterine bruit was heard and milk was found in the breasts. The patient had felt movements "high up" for six or seven weeks. On February 3 the fœtus had been active and the uterus was the size of a six months' pregnancy; the date of confinement was calculated by size as May 3. On May 1 the patient had a spontaneous uncomplicated delivery of a living male infant, weighing six pounds thirteen and a half ounces; the child was breast fed and increased in weight to seven pounds five ounces before the patient's discharge from hospital. The first stage of labour lasted ten hours, the second stage half an hour, and the third stage fifteen minutes; the fœtus was delivered in the left occipito-anterior position. No menstrual period and no loss of blood occurred after the dates in June already given.

Discussion.

The patient was under observation from October 7, 1937, for seven months. If her pregnancy is counted from June 8, it lasted for 327 days; if it is counted from June 15, it lasted for 320 days. Her next baby was born on April 17, 1939, thirteen days late.

I have encountered one other case in which a pause occurred in the growth of the fœtus and the heart sounds disappeared for a few days; that infant was born prematurely and lived. In the case reported the prolonged pregnancy was apparently due to a pause in the growth of the fœtus which lasted for six weeks or so; labour took place forty-seven days later than the date originally expected. Perhaps the poor diet had something to do with the condition. Apart from the medico-legal importance of so long a pregnancy, the patient being under observation for nearly seven months, this case gives a clinical demonstration of the wisdom of waiting for a time before terminating a pregnancy when the fœtus is thought to be dead.

Reviews.

TOMOGRAPHY.

THE tomograph seems to have found its chief field of usefulness in the radiography of the lungs, especially on account of its ability to delineate cavities obscured in simple skiagrams by the shadow of fluid, of thickened pleura or of the bones of the thorax. This is reflected in J. B. McDougall's volume entitled "Tomography", which is mainly an atlas illustrating the uses of tomography as an aid to clinical judgement in pulmonary tuberculosis.[1] The book gives a brief outline of the principles of tomography and of the technique of the method. There follow 110 illustrations, well reproduced in gravure; most of these show side-by-side skiagrams and tomograms of the chests of some twenty-five persons suffering from pulmonary tuberculosis, and there are also a few miscellaneous tomograms from the collection of the late E. W. Twining. A summary and bibliography complete the volume. The British price of one guinea seems very little for a book of this kind, so well made.

ENDOCRINOLOGY OF THE REPRODUCTIVE SYSTEM.

IT would perhaps have been better if the publishers, instead of the title "Recent Advances in Sex and Reproductive Physiology",[2] had employed the designation "Recent Advances in the Endocrinology of the Reproductive System", for the treatment has been confined to this field—wisely so, the reader will conclude, as the material is so abundant and recent progress has been so rapid. Recognizing the true scope of the book, we can welcome it as fit to take its place amongst the best of the "Recent Advances" series. On first taking up the book we looked up a few special subjects as criteria—the action of light on the gonads, the Xenopus test for pregnancy, the gonadotrophic content of the pituitary at the menopause and, of course, the relation between the menstruation of primates and the œstrous cycle in lower animals. As these were all well presented, the careful systematic study of the book was undertaken with pleasure, though, as the pages are packed with matter, critical reading was slow. This is the second edition, and large sections of the book have been rewritten; also new chapters have been added. To attain balance when research in this field is so active and the results of such research are occasionally divergent in the hands of different investigators required sound judgement, and this is evident. There is a singular avoidance of chemical constitutional formulæ. Now that the unfortunate tradition of emphasizing physical and metallic chemistry in the medical curriculum has been broken, the younger generation of medical men are more at home in sterol and similar formulæ than their predecessors. But possibly the reason for the omission was a matter of printing costs. The use of hormonal therapeutic agents is given with commendable restraint and clarity. Possibly to many readers the most interesting and least known conclusions are concerned with the effects of hormonal excess. Each chapter has an excellent bibliography. The illustrations are on the dark side and could be improved, but apart from this small matter the book is most welcome.

[1] "Tomography", by J. B. McDougall, M.D., F.R.C.P., F.R.S.E.; 1940. London: H. K. Lewis and Company Limited. Demy 4to, pp. 73, with 110 illustrations. Price: 21s. net.

[2] "Recent Advances in Sex and Reproductive Physiology", by J. M. Robson, M.D., D.Sc., F.R.S.E., with an introduction by F. A. E. Crew, M.D., D.Sc., F.R.S.; Second Edition; 1940. London: J. and A. Churchill Limited. Demy 8vo, pp. 342, with 62 illustrations. Price: 15s. net.

The Medical Journal of Australia

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GENERAL PRACTITIONERS AND CLINICAL PATHOLOGISTS.

No group of those who follow the call of medicine are more jealous of their rights than the general practitioners. For many years past they have time and again had filched from them portions of what they quite legitimately regarded as their preserves. Sometimes a government department has been responsible, deciding in its paternal wisdom that certain health services should be a charge on the public purse or that certain groups of persons should receive medical attention without cost to themselves. Sometimes perhaps the deprivation has followed the growth of medical knowledge—research and experience have been so fruitful that a specialty has arisen where formerly the general practitioner was all sufficient. Some practitioners have from time to time expressed fears that specialism will supersede general practice and that their living will be taken from them. It is useless to tell these lugubrious persons that general practitioners are the backbone of medicine, and that, come what may, the man who takes the whole of medicine for his field will always be indispensable. They are as determined as a certain type of woman who enjoys bad health; but they do not represent the majority of practitioners. Those who know nothing of medical practice will be at a loss to understand why a general practitioner should be so jealous of his rights as he is. They will argue that the scope of medicine is so wide that the general practitioner should welcome rather than oppose any curtailment of his sphere of activity. These people do not realize that whether he undertakes the treatment of patients in every branch of medicine or not, the general practitioner must know something of each of these branches. This knowledge must not be superficial, for he has to decide the nature of the condition from which his patient is suffering. He must know whether the condition is self-limiting or whether prompt measures to save life have to be undertaken. In short, he must make a reasonably accurate diagnosis. He must then decide whether the treatment comes within the scope of his activities or whether the patient must be handed over to the care of a specialist. The general practitioner holds that, having diagnosed the illness of his patient, he should be allowed to carry out any treatment that comes within the range of his ability. If this contention is analysed it will probably be found to be due to two factors. In the first place the general practitioner has to earn his living; as long, therefore, as he can do the work and further the welfare of his patient in the doing of it, he is naturally resentful of anyone who would restrict his activities. The second reason why the practitioner wishes to see his patient through his illness, and one that operates much more than people may think, lies in the absorbing interest that permeates the whole of medical practice—that associated with the reaction of the human body to disease and of the human mind to altered body conditions. There is in very truth no occupation so full of human interest as that of a general practitioner of medicine.

We have shown that, as society is constituted at present, the general practitioner is justified in his zealous championship of his rights, and we think that most reasonable people will appreciate his point of view. Reference has been made to this subject, however, not to lay emphasis on the important place that the general practitioner takes in the present scheme of things, though that were worthy enough an object. Rather would we suggest that general practitioners ask themselves whether they are as considerate of the rights of certain other practitioners as they would have others be about theirs. The reference is to clinical pathologists, that band of unobtrusive workers who make many a diagnosis for general practitioners when they are groping blindly and do not know which way to turn, who seldom come before the public, and who for some reason or other do not stand up for their rights as the general practitioners do. Among clinical pathologists are included pathologists proper, bacteriologists and biochemists. Most general practitioners have recourse in their everyday work to clinico-pathological examinations; if they do not, they either are possessed of extraordinary powers of divination or are not doing the best for their patients. The extent of the investigations that may be undertaken by the clinician himself depends entirely on the time at his disposal, on his inclination and his technical ability. Some years ago a long argument took place in this journal on this subject. On the one hand it was held that the clinician could and indeed should carry out for himself such investigations as a full blood count, the quantitative estimation of the constituents of urine and the microscopic examination of urinary deposits, the examination of smears for certain organisms, and so on. Others held that it was no part of a clinician's task to do these things. The fact remains that many practitioners, particularly in the country, do undertake for themselves many examinations of this kind. But even these practitioners find that certain investigations have to be passed on to the clinical pathologist.

The clinical pathologist has rights. It is not intended to discuss these in detail, but to make strong reference to his right to be paid for his services by those who can afford to pay him. The general practitioner who is so

insistent on his own right to be paid is often responsible for the non-payment of the clinical pathologist. The work done at hospitals and by government departments is also partly responsible. Patients are being sent to the pathological departments of certain hospitals by outside practitioners to have investigations carried out. If the patients cannot afford to pay even an intermediate fee to a private clinical pathologist, there may be no objection to this. The same may be said of government departments. Some idea of the enormous number of pathological examinations that are carried out may be gathered from the fact that during 1938 a total number of 92,713 examinations were made at the Bureau of Microbiology of the New South Wales Department of Public Health. Of these, 15,325 examinations were carried out for private practitioners. The practitioners who sent these 15,325 patients or their specimens to the Bureau of Microbiology would do well to ask themselves how often they have dealt in this way with a patient who was not impecunious—in other words, how often they have deprived a brother practitioner of his just fee. What an outcry there would be if pathologists saw the patients first, took fees from them and then sent them for treatment to the out-patient departments of public hospitals. It has lately been reported on reliable authority that general practitioners treating patients who pay full fees, have sent these patients without thought of private pathologists to the out-patient departments of public hospitals that they may have pathological examinations made. To correct practices of this kind will be difficult; the thoughtless or selfish practitioners who exploit the pathologist (we do not believe that they are many) can so easily continue in their unworthy ways. It is to be hoped that the pathologists themselves will make their voices heard in their own defence.

Current Comment.

BLAST INJURIES OF THE LUNGS.

THE effects on the lungs of blast from high explosives have been studied experimentally by S. Zuckerman at the instance of the Research and Experiments Department of the Ministry of Home Security of Great Britain.[1] During the war of 1914-1918 some men who were close to the explosion of a shell or bomb died without any apparent wound. Obviously, if the authorities are to prevent deaths of this kind or to mitigate the effects of the blast from an explosion, they must understand what happens in the thorax when death from the blast of an explosion occurs. That this type of injury should be made the subject of a special inquiry is typical of the thoroughness which we should all like to see in connexion with the prevention and treatment of all traumatic conditions associated with war that are not properly understood. Zuckerman defines blast as the compression and suction wave set up by the detonation of high explosive. In the neighbourhood of an explosion there occurs a momentary wave of high pressure, and this is followed by a negative suction pressure, caused by the fact that the positive compression wave has reduced the density of the air behind it to below the normal atmospheric pressure. The compression wave is due to the hydrostatic pressure of the compressed gas, which acts equally in all directions. Since a shell is moving rapidly, it exerts, in the direction of motion only, an additional wind pressure on objects in its path. The wave of pressure, which is highest in the region of the explosion, becomes rapidly less the further it moves away. Zuckerman states that fifteen feet from the explosion of a 125-pound charge the hydrostatic pressure may be of the order of 200 pounds per square inch, whereas fifty feet away the maximum pressure recorded will not be more than ten pounds. Close to the explosion the wind pressure may be as great as the hydrostatic pressure. The suction component of the blast wave is always much weaker than the pressure component, and it can never be greater than 15 pounds per square inch, since this corresponds to a perfect vacuum.

When a bomb explodes, a man may be hit by a piece of the bomb-casing or by some structure displaced by the bomb in its explosion; he may be thrown violently down; he may be affected by the blast wave. Zuckerman states that workers have speculated on the basis of pulmonary lesions following a blast. Three possibilities have been suggested. The first is that the lesions are due to the lowering of alveolar pressure by the suction wave acting through the respiratory passages, with consequent rupture of the alveolar capillaries. The second is that the lesions are caused by the distension of the lungs with air. The third possibility is that the lesions are due to the impact of the pressure wave on the chest wall. Zuckerman records a series of animal experiments that suggest the truth of the third of these possibilities. He exposed mice, rats, guinea-pigs, rabbits, cats, monkeys and pigeons in the open to blast from the explosion of charges of seventy pounds of high explosives and from the explosion of hydrogen and oxygen in balloons. In the high explosive experiments animals were killed at distances of 13 to 18 feet from the explosion; in these circumstances the positive pressure (the hydrostatic pressure) varied between 126 and 62 pounds per square inch. No animal received any injury if it was more than 50 feet from the explosion. In no animal was there any sign of external injury, and the outstanding lesion was bilateral traumatic hæmorrhage in both lungs, varying in degree according to the distance of the animal from the charge. Zuckerman describes the post-mortem appearances and illustrates his remarks by pictures of specimens and reproductions of photomicrographs. Interest centres chiefly in the microscopic appearances. In areas where damage was not of severe degree, there were zones in which the alveoli and the smallest bronchial tubes were filled with blood. The alveolar walls were often disrupted, the hæmorrhage originating in the torn capillaries; interstitial hæmorrhage was also present. In the severe grades of damage large areas of the lung were disrupted and hæmorrhagic, and the larger bronchial tubes were filled with blood. Whenever the animal was killed by the explosion blood was present in the upper respiratory passages. In the balloon explosion experiments similar lesions were caused, except that the lesions were unilateral when the animals were so close to the balloon that the exposed side shielded the other. The proof that the lesions are mainly due to the impact of the blast wave on the body wall was afforded by the observation that when the bodies of the animals were clothed in thick layers of rubber little or no damage was caused compared with the controls. If only one side of the animal's trunk was clothed in rubber, lesions followed when the uncovered side faced the explosion; but when the covered side was turned to the explosion, damage was absent or very slight.

Complementary to Zuckerman's report is an account of the clinical effects of high explosive blasts on the lungs that comes from D. M. Dean, A. R. Thomas and R. S. Allison.[1] In the series reported by these observers are 27 cases. Twenty-one of the patients had suffered from extensive superficial burns; three had been immersed in the sea. The authors discuss only the conditions found in the chest. All but two of the patients had been directly exposed to heavy blast at relatively close quarters. Only six patients manifested chest symptoms such as cough and expectoration; in one instance shortness of breath and general restlessness were present. The symptoms appeared between the second and fifth days; never on the

[1] *The Lancet*, August 24, 1940.

[1] *The Lancet*, August 24, 1940.

day of exposure to the blast. In sixteen instances abnormal physical signs were present and fourteen patients manifested abnormal radiological appearances. In only two of these fourteen cases were the radiological changes obvious. The appearances were mostly similar to those associated with an early pleurisy. From the short account given of these patients it must be concluded that the lungs were not affected in every instance. That is not really of great importance. The importance lies in the conclusion stated by Dean, Thomas and Allison that, as far as they can determine, the physical signs to be expected are diminished movement of the diaphragm, fullness of the chest giving it an emphysematous appearance, and impairment of resonance at one or both bases, with or without crepitation. One curious manifestation noted in many instances was a "blown-up" or ballooned appearance. Beyond stating that this appearance was often associated with diminished movement of the diaphragm, Dean and his fellow workers can offer no explanation for it. It is a pity that they were not able to include in their observations one or two cases in which death had followed exposure to a blast from an explosion. For a description of such a case the reader must turn to Zuckerman's paper. The case mentioned by him is one of S. T. Falla's and is reported in full in *The British Medical Journal* of August 24, 1940. Zuckerman reproduces photomicrographs from this case and shows that in some respects the lesions are similar to those produced experimentally. Falla in his account of the post-mortem appearances describes the cut surface of the lung as "a miliary condition of unmistakable fresh hæmorrhages".

Several practical points emerge from these papers. As is pointed out in a leading article in *The Lancet* of August 24, 1940, there is a danger that the condition may go unrecognized on account of the indefinite physical signs and the delay that occurs before symptoms make their appearance. It is pointed out that if the cause of asphyxia in these cases is not recognized, the Schafer method of artificial respiration may be used with ineffective and even harmful results. There also arises the question of shelter in air raids, and *The Lancet* wisely urges the adoption of the approved prone position on the ground, preferably behind some substantial structure. Perhaps the question of diagnosis of lung injury after exposure to a blast is most important. Da Falla points out that diagnosis of damage to the lung by explosion blast can be made if blood-stained fluid appears in the mouth or nose without apparent cause; but he also insists that further investigation is desirable. When he wrote he was aware of Zuckerman's work and of the general trend of its results. He wishes, however, to have three lines of investigation made. The first is a clinical study of patients; this should include not only the symptoms and signs, but also the results of different types of treatment. Secondly, he would have post-mortem examinations done on all persons killed in air raids; this we fear would often be impracticable, however important it might be from the scientific point of view. Thirdly, he would have radiological examinations made of the chests of all persons who have been near a bomb explosion. This again is a counsel of perfection. At the same time, further X-ray studies are necessary, even if only to investigate the "bruised pleura" described by Dean, Thomas and Allison in relation to diagnosis and the area of the body exposed to the blast.

THE X-RAY SHADOW OF THE HORIZONTAL INTERLOBAR FISSURE IN TUBERCULOSIS OF THE RIGHT LUNG.

PHYSICIANS who are accustomed to examining the X-ray films of the chests of their tuberculous patients do not fail to observe any slight upward migration of small lesions situated in the upper lobes of the lungs; they are well aware that the import of such migration, which is attributed to shrinkage of the affected lobe by a fibrotic process, is rather favourable than otherwise, and is usually associated with manifest improvement in the patient's health. B. H. Y. T'ang and Chien-Liang Hsu, of Peiping, have recently suggested a much more delicate and more exact means of detecting fibrotic shrinkage when it occurs in the upper lobe of the right lung, and they have reported a study of the relationship of the position of the horizontal interlobar fissure to prognosis in pulmonary tuberculosis.[1]

It is stated by T'ang and Hsu that the horizontal interlobar fissure (which they call the transverse fissure) is visible in postero-anterior skiagrams in 69·2% of persons who present no evidence of pleural or pulmonary disease; however, it has been recently stated by P. T. Knies[2] that the fissure is visible in only 20% of normal persons, though in more than 50% of those suffering from pulmonary tuberculosis. T'ang and Hsu state that when a standard technique is used in the preparation of chest films a normal shape and position for this fissure can be established and deviations from the normal can be appreciated and measured, and that their experience has shown them that a small upward or downward displacement of the X-ray tube at the usual distance from the film carrier produces an insignificant change in the position of the fissure. From a study of X-ray films of the chests of fifty healthy persons, T'ang and Hsu state that normally the shadow of the horizontal interlobar fissure should appear as a horizontal hair-like line, either straight or with an upward convexity of less than a centimetre, dividing the total area of the right lung field into very nearly equal parts: its medial end usually lies at the level of the third costal cartilage or the interspace below it. When serial skiagrams of the same patient are examined side by side and measured, slight changes in the position of the horizontal interlobar fissure can be readily observed, even though slight deviations from normal may not be appreciable in single films. Disease of any considerable extent will, by lessening the elasticity of a lobe, make it appear small in comparison with the healthy lobe when the films are exposed during full inspiration; any extensive raising of the interlobar line, especially when this is progressive in the course of pulmonary tuberculosis, must represent a diminution in the size of the right upper lobe, and as such it becomes an index of healing. T'ang and Hsu followed for at least a year the progress of one hundred persons suffering from tuberculosis affecting only or mainly the upper lobe of the right lung and in whom the horizontal fissure could be observed radiographically. In 44 the fissure was displaced upwards at the time of the first X-ray examination or became displaced upwards during the observation period, and in 42 of these progress was satisfactory, the disease being arrested in an average time of one and a half years from the first observation; in 51 no change from the normal shape of the fissure could be determined, and in only 18 of these was progress satisfactory; in five a persistent downward displacement of the fissure occurred, and none of these patients did well.

T'ang and Hsu point out that the type of lesion found in the tuberculous lobe above the horizontal fissure does not of itself affect the position of the fissure to any great extent. Thirty-seven of their patients had lesions chiefly fibrous in character, and in only 17 of these was the fissure displaced from normal; cavities were present in 14 of the patients, and in nine the fissure became displaced, pleural adhesions being demonstrated in four of the others. It is suggested that if much of the periphery of the diseased lobe is fixed and it cannot shrink despite fibrosis, in which circumstance the interlobar fissure will not rise, the outlook is unfavourable.

The simple clinical method elaborated by T'ang and Hsu is thus more than a demonstration of the latent healing power of Nature reflected in fibrosis; it may be used to help stave off or strengthen the physician's presentiment that this healing power may find its task a very difficult one without the aid of timely surgery.

[1] *Tubercle*, May, 1940.
[2] *Radiology*, March, 1940.

Abstracts from Medical Literature.

PHYSIOLOGY.

Carbon Monoxide Anoxæmia.

ESTHER M. KELLICK (*Physiological Reviews*, July, 1940) has reviewed the subject of carbon monoxide anoxæmia. The effects of breathing carbon monoxide are discussed together with the mode of action of the gas. The symptoms of carbon monoxide anoxæmia in man are described; the percentage saturation of the blood with carbon monoxide which produces these symptoms is also given. Figures are supplied allowing the probable effects of exposure to different concentrations of the gas for any specified time to be predicted. Innumerable clinical records of carbon monoxide poisoning have been described in the literature, with a multiplicity of after effects, most of which represent the effect of anoxæmia on various parts of the body. Although the central nervous system has been shown by many workers to exhibit gross changes of many types in carbon monoxide poisoning, only 39 patients out of a total of 21,143 persons affected by carbon monoxide poisoning showed any mental or neurological after-effects. All of these 39 patients had been severely poisoned; all were unconscious when found, 14 being described as *in extremis*. There seems little evidence that susceptibility to infection is increased on exposure to the gas. The effect on the cardio-vascular system is of interest also from the medico-legal aspect, since collapse and death hours after exposure may occur in circumstances suggesting foul play. The effect on metabolism and respiration, and the chemical changes occasioned in blood are also discussed. Under the heading of reproduction and sex glands mention is made of the fact that after an animal is poisoned its fertility is diminished, and that men surviving acute poisoning are sometimes rendered impotent. The possibility of acclimatization to at least the lower range of concentrations seems to have been conclusively demonstrated, although the means by which this acclimatization is brought about is not yet known. In conclusion the methods recommended for the clinical treatment of carbon monoxide poisoning are reviewed.

Typical Anaphylaxis in the Dog in the Absence of the Liver.

E. T. WATERS AND J. MARKOWITZ (*The American Journal of Physiology*, August, 1940) describe their success in the production of typical anaphylactic shock in sensitized dogs after complete surgical removal of the liver. Anaphylaxis in the dog is characterized by hepatic engorgement, and it is generally accepted that anaphylaxis does not occur in the dog in the absence of the liver. It is supposed that responses in extrahepatic tissues are dependent upon the primary reaction in the liver and are the result of the liberation therefrom of toxic material into the circulation. Only in one previous paper have two workers claimed to have obtained anaphylactic shock after exclusion of the liver; but their results do not represent the typical profound fall in blood pressure of the intact shocked dog. These experiments, in which exclusion of the liver was attempted by ligation procedures, may, the authors state, be criticized on the grounds that this organ was not completely isolated from the circulation. Using injections of India ink, Rich has shown that some connexion between the liver and the general circulation still exists by means of certain diaphragmatic vessels, when ligatures are placed around the portal vein, the hepatic artery and the inferior *vena cava* above the diaphragm. In the authors' work the liver was completely removed from the body. The dogs were sensitized to horse serum treated with alum. The shock dose of serum was given about five weeks later, after surgical removal of the liver, and the presence of shock was deduced from the effect on blood pressure and bladder tone. Their results support the original conclusions of Biedl and Kraus that the fall in blood pressure is due to a peripheral vasodilatation. The tonic contraction of the bladder has been stated to be due to the liberation from the liver of an anaphylatoxin; but the authors have obtained bladder contraction in the absence of the liver.

Variation of Blood Pressure with Brief Voluntary Muscular Contractions.

E. JACOBSON (*The Journal of Laboratory and Clinical Medicine*, July, 1940) describes the changes which may be produced in the systolic and diastolic blood pressures by various brief voluntary muscular contractions, such as clenching the fist. The evidence obtained from previous work pointed clearly to a relationship between the contraction in the manifold muscle groups of the individual and his blood pressure. In physical exercise the systolic pressure rises during vigorous muscular contraction, at least until fatigue sets in, although Fishberg found that slight muscular exercise produced little change in the blood pressure. Blood pressure tends to fall with progressive muscular relaxation, especially as this nears completion; but mere prolongation of the rest without an increase in the degree or extent of relaxation does not necessarily effect an additional fall in pressure. While it is certain that skeletal muscles do not necessarily relax fully during a period when an individual attempts to rest, there is still a tendency to identify lying down with relaxation. The blood pressures were determined with a "Tycos" self-recording sphygmomanometer, whilst the observations of muscle tension were made by measuring the action potentials with two string galvanometers in various muscle groups, such as the *biceps brachialis*, *quadriceps femoris*, the abdominal muscles or those of the eye. A composite graph of the results of fist clenching in seventy subjects shows in less than five minutes a rise in systolic and diastolic pressures of about seven millimetres of mercury, the maximum being obtained after seven minutes with a systolic rise of eighteen millimetres and a diastolic rise of twelve millimetres. A number of clinical cases are reviewed. In a relaxed individual successive contraction and relaxation of a muscle group are frequently accompanied by corresponding rises and falls of both pressures. The extent of the relative rise or fall depends not only upon the intensity of the particular voluntary contraction, but also upon the degree and extent of relaxation present in the general musculature. No contrasting rise may be obtained if the subject is not well relaxed before he clenches his fist. Additional contraction in other groups promotes further rise in blood pressure.

The Comparative Effects of Large Doses of Some Calcium Salts.

E. R. B. SMITH (*The Journal of Laboratory and Clinical Medicine*, July, 1940) describes experiments indicating the non-toxic nature of calcium gluconate-idonate in intravenous calcium therapy. This salt is soluble to the extent of 411 grammes per litre at 25° C., the calcium content of the salt being 9·3%. Idonic acid is derived from the hexose sugar idose and is isomeric with gluconic acid. Calcium chloride, calcium gluconate and calcium gluconate-idonate were administered to rats by means of a stomach tube, in amounts equivalent to 0·4 gramme of calcium per kilogram of body weight daily for seventy days. Five of the original ten in the group that received chloride died, while the other groups survived intact. Administration of one gramme of calcium per kilogram of body weight was fatal in all cases with the chloride, but when calcium was given as gluconate-idonate, four out of ten survived the entire period. Solutions of the three salts were injected into the femoral vein of dogs, the concentration of calcium in the serum was determined and electrocardiograms from Lead II were taken at frequent intervals during the injection. Calcium chloride when given orally to rats or intravenously to dogs proved to be more toxic than calcium gluconate or gluconate-idonate. The two organic salts vary little in their toxicity for dogs and rats. Intravenous injection of 0·2 molar solutions carried on to the point of cardiac arrest (usually with ventricular fibrillation) revealed no differences between the effects of gluconate and calcium gluconate-idonate.

The pH Value of the Blood and Changing Meteorological Conditions.

M. BERG, A. MAYNE AND W. F. PETERSEN (*The American Journal of Physiology*, July, 1940) describe the results of weekly determination of the pH value of the blood of a group of six dogs, carried on for one year. The determinations were made with a glass electrode and venous blood with frequent standardization, and results were checked at intervals with a microchamber electrode, blood straight from the vein being used. The dogs were fed on a standard diet. Groups of four to six human beings were studied daily for two months and the results were compared with those of the dogs. A high correlation was found in the pattern and in the degree of variation of the pH of the blood among the group of dogs throughout the year. A high statistical correlation was obtained on comparison of the continuous pH values in the group of dogs with those of the group of human beings. A relatively wide degree of fluctuation was observed in both human beings and dogs. In man the weekly averages varied from 7·28 to 7·68, while in the dogs they varied from 7·32 to 7·68. In comparing pH and weather conditions statistically, the authors found significant coefficients with barometric pressure and with temperature, with a distinctly higher correlation for barometric pressure than for temperature. Increases in pH value were

associated with increases in barometric pressure. Only at higher temperatures were increases in pH definitely associated with increases in temperature. When an attempt was made to evaluate seasonal influences, varying results were found, depending upon the weather indices discussed.

BIOLOGICAL CHEMISTRY.

Diet of Miners Free from Nystagmus.

C. E. KELLETT (*Journal of Hygiene*, July, 1940) has investigated the vitamin *A* content of the diets of a group of forty Durham miners, who despite many years of underground work, had never suffered from nystagmus. The diets differed substantially from that of the general population of England, in that the vitamin *A* content was high. The high intake was considered to be conditioned by their manner of working under poor illumination. The large and single source of vitamin *A* was butter. The average daily intake of vitamin *A* was 6,600 units. The addition of further quantities of vitamin *A* to the diet produced no material improvement in the miners' power of dark adaptation. The excellent health of the miners investigated and the freedom from nystagmus or other defects of vision were held to be good reasons for endeavouring to maintain in miners a high daily intake of vitamin *A*.

Liberation of Renin by the Kidney.

K. G. KOHLSTAEDT AND IRVINE H. PAGE (*The Journal of Experimental Medicine*, August, 1940) perfused isolated dogs' kidneys with defibrinated blood under hæmodynamic conditions similar to those in the body. In these circumstances blood flow, urine excretion and oxygen consumption were well maintained, but urea clearance was low. Renal venous blood collected initially and at the end of three or more hours of perfusion exhibited no difference in vasoconstriction properties when perfused together with renin or renin-activator through an isolated rabbit's ear. Reduction of pulse pressure by constriction of the renal artery was performed, without significant reduction of the mean pressure. Renal venous blood collected after about one hour of perfusion with reduced pulse pressure differed from that collected before reduction of pulse pressure, in that it caused intense vasoconstriction when perfused with renin-activator through an isolated rabbit's ear. These results indicated that kidneys perfused under normal hæmodynamic conditions liberate little renin, while reduction of pulse pressure appears to be the stimulus eliciting the outpouring of renin. Reduction of blood flow follows, but appears to be an effect rather than the cause of the increased liberation of renin.

Vasoconstrictor Action of Plasma in Hypertension.

IRVINE H. PAGE (*The Journal of Experimental Medicine*, September, 1940) has studied the vasoconstrictor action of plasma from patients with essential hypertension, malignant hypertension and chronic nephritic hypertension, and that of four dogs made hypertensive by experimental perinephritis or constriction of the renal artery. Used as a perfusing medium in an isolated rabbit's ear, these three samples of plasma caused marked vasoconstriction when added in small amounts to blood from a dog. In the same circumstances normal plasma from man or dog caused little or no vasoconstriction. Plasma removed from peripheral vessels of hypertensive dogs caused more marked vasoconstriction than that from the renal veins. A similar result was obtained with plasma from one hypertensive patient. It is considered that the vasoconstriction is the result of the presence of angiotonin in the peripheral blood, since renin is liberated into the renal vein in large amounts in hypertensive dogs and reacts with renin-activator to produce angiotonin, and since the conditions of the experiment are such as to enhance greatly the sensitivity of the ear preparation to angiotonin. Since vasoconstriction occurs under the same experimental conditions with plasma from both hypertensive patients and dogs, it is considered that the chemical mediator of both is similar and is possibly angiotonin.

Choline and the Vitamin B_2 Complex.

PAUL GYÖRGY AND HARRY GOLDBLATT (*The Journal of Experimental Medicine*, July, 1940) have presented data illustrating the importance of choline as a potential member of the vitamin B_2 complex. In rats kept on a basal diet deficient in vitamin *B* and supplemented with thiamine and riboflavine, the only lesion which could be attributed to deficiency of choline was fatty infiltration of the liver. The addition of vitamin B_6 to this diet aggravated the deficiency of choline and resulted in the appearance of additional lesions of cortical necrosis of the kidney. The lesions of the liver and kidney were indistinguishable from those previously attributed to experimental cystine intoxication. While the determining factor for the need of choline has been found in the cystine/methionine ratio of the diet, these experiments showed that this ratio is not a fixed figure, but may be profoundly influenced by other factors, such as the vitamin B_6 content of the diet. Attention is drawn to the possible identity of these renal lesions in rats, with bilateral symmetrical cortical necrosis of the kidneys, which occurs in human beings, especially in pregnant women.

Effect of Sulphanilamide on Acid-Base Metabolism.

W. W. BECKMANN, E. C. ROSSMEISL, R. B. PETTENGILL AND W. BAUER (*The Journal of Clinical Investigation*, July, 1940) have presented the results of an examination of the changes in the acid-base excretion and in the electrolyte structure of the blood serum during sulphanilamide administration, and of the relationship of increased lung ventilation to these changes. There was a large loss of sodium accompanied by a smaller loss of potassium and little or no loss of chloride ion. The concentration of sodium in blood plasma was reduced to the extent of four to five millemol equivalents per litre. The loss of sodium was much larger than the reduction of its serum concentration indicated, and therefore presumably involved a considerable withdrawal of extracellular water. The concentration of chloride was increased to the extent of five to six millemol equivalents per litre above the initial value. The changes in acid-base excretion and in electrolyte structure of plasma occurred within one to three days of the start of sulphanilamide administration. The altered values were maintained until sulphanilamide was removed, and then the initial losses of sodium and potassium were rapidly recovered and the normal electrolyte pattern of plasma was restored. Observations on respiratory exchange, serum alterations and removal of sodium in the urine at short intervals following ingestion of a single large dose of sulphanilamide showed that the entrance of bicarbonate into the urine was an almost immediate event, which was followed by a gradual increase in lung ventilation. This hyperpnœa was regarded as a secondary event compensatory to plasma bicarbonate reduction caused by removal of fixed base in the urine.

Vitamin C Excretion.

G. F. FRIEDMAN, S. SHERRY AND E. P. RALLI (*The Journal of Clinical Investigation*, September, 1940) have studied the excretion of vitamin *C* in subjects with low plasma vitamin *C* concentrations. This work supplements an earlier study on subjects with normal or artificially elevated plasma concentrations. It was observed that the excretion of vitamin *C* was determined by the plasma concentration, the rate of glomerular filtration and the rate of tubular resorption, and that, as the resorptive mechanism was limited by a maximal rate, when the vitamin was presented to the tubules by the glomerular filtrate at a rate exceeding this maximum, the excess was excreted in the urine. The observations at lower plasma vitamin levels, varying from 0·03 to 2·05 milligrammes *per centum*, show that the resorption is never complete and that the clearance of vitamin *C* at low plasma levels is constant and independent of the plasma concentration. As the plasma concentration rises and approaches the value for the maximal rate of tubular resorption, the excretion of vitamin *C* rises rapidly, and at very high plasma levels the vitamin *C* clearance approaches the inulin clearance.

Spontaneous Disintegration of Hæmoglobin.

N. H. FAIRLEY (*The British Journal of Experimental Pathology*, August, 1940) has investigated the spontaneous disintegration of oxyhæmoglobin and methæmoglobin. It was found that *in vitro* there were three stages demonstrable in the katabolism of hæmoglobin incubated in the presence of human plasma: the production of neutral and alkaline methæmoglobin, the splitting of methæmoglobin into globin and hæmatin (ferric) and, finally, the coupling of hæmatin to serum albumin with the formation of methæmalbumin. After intravascular hæmolysis in man the portion of the free circulating hæmoglobin which is not excreted in the urine or absorbed by the reticulo-endothelial system persists in the circulation and gives rise to methæmalbumin and not to hæmatin. The author suggests a possible route for the disintegration of circulating hæmoglobin in the hæmoglobinurias and hæmolytic anæmias: Hæmoglobin is split into globin and reduced hæmatin (ferrous); reduced hæmatin is oxidized to hæmatin (ferric); hæmatin (ferric) is coupled with serum albumin to form methæmalbumin.

Special Articles on Psychiatry in General Practice.

(Contributed by request.)

XXII.

TREATMENT BY INSULIN SHOCK AND INDUCED CONVULSIONS.

In an age of greater faith the devils of mental disease were dispelled by prayer. Draughts of holy water from the church bell brought comfort to distracted spirits while peony and mugwort helped to rehabilitate reason in the tottering citadel of the mind. Beyond the power of prayer, recalcitrant devils were subjected to whipping and ducking. And when demonology suffered its final eclipse, science supplanted superstition without providing any rational therapy for mental illness. Physicians, unable as they were to "minister to a mind diseased", recommended the natural hydrotherapy of the sacred wells or, throwing "physic to the dogs", took refuge in a therapeutic nihilism which characterized psychiatric practice until quite recent times.

Fresh hopes for the effective treatment of mental disorders have arisen since Sakel introduced his hypoglycæmic shock method, which has in the past few years gained wide acceptance throughout the civilized world. Sakel has never been at pains to hide the empirical nature of his treatment, which is still in the early experimental stage and which is undergoing modifications almost from month to month in the hands of its numerous enthusiasts.

Insulin Hypoglycæmia.

Insulin shock was introduced for the treatment of schizophrenic patients, and it still finds its chief application in this sphere. Broadly speaking, the aim is to administer insulin to the patient each day in gradually increasing doses until the stage of coma is reached. The patient is allowed to remain in the comatose state for a period of from one-half to two hours. Glucose is then administered in a quantity sufficient to counteract the effect of the insulin; and this may be done either by a nasal tube or by the intravenous route. By the former method the patient awakens from coma in from fifteen to thirty minutes, while in the latter instance the patient should awaken in a few minutes. The whole procedure, from the initial early morning administration of insulin until the time of final awakening is approximately five hours. Shortly after the patient wakes up, a light carbohydrate meal is given, after which the patient may be allowed to get up and dress and so pass the remainder of the day with friends or at an occupational therapy class.

In such a bare outline the insulin technique sounds the essence of simplicity, whereas in actual practice it may become both complicated and hazardous, as practically every patient reacts differently to the administration of insulin. Coma comes to some patients after small doses; to others it comes only after the administration of three or four hundred units of insulin. Some pass through a stage of preliminary restlessness in which the psychosis may seem to be reactivated. The reaction often varies from day to day in the same patient, even when the same amount of insulin is administered. The coma may be light or deep. The patient may wake spontaneously or the coma may deepen with such alarming rapidity as to call for the intravenous administration of glucose. Signs of collapse may show at any time. Epileptiform seizures may develop without warning and many minor complications may arise in the course of the morning's treatment, which make it imperative that the doctor shall be in constant attendance upon the patient during the whole period of insulin intoxication.

The results obtained by Sakel and his co-workers in the Vienna clinic during the first year in which insulin was used, were truly remarkable. There can be no doubt that they were to a certain extent influenced by the enthusiasm which a new and promising form of treatment had naturally invoked, and under the stimulus of such enthusiasm each individual patient received a great deal more personal attention from both nursing and medical staffs than would be the case at a later time, when the treatment was more widely established and firmly accepted. But when due allowance is made for enthusiasm and increased personal attention, it can be seen that insulin therapy has produced more brilliant results in schizophrenia than any other treatment hitherto exploited. In early cases, in which the psychotic state had not been manifest for more than six months, a remission of 75% was claimed. In cases of longer duration where the psychosis had been apparent for from six to eighteen months, about 60% of patients achieved a remission through insulin. In unselected cases, in which the disease had been in process for more than two years, a 40% remission was registered. This latter figure is at least twice as high as the figure generally claimed for spontaneous remissions in unselected cases of schizophrenia. The mortality rate is very low and with due care and wide experience accidental death through insulin is almost unknown.

The treatment of schizophrenic patients with insulin is not only in itself intricate, but may also be long and arduous. It was early recognized that the insulin *per se* was not the only therapeutic instrument and that it alone would not serve to bring about a large number of remissions. The pharmacological shock induced by insulin is held to be the agent which brings the patient back to reality and puts him in touch with the physician. A certain amount of simple psychotherapy carried out at the bedside and later in longer talks with the physician is essential, and the value of occupational therapy carried out in conjunction with the insulin treatment cannot be over-estimated.

It is customary to give insulin each day of the week for six days, to make the seventh day one of rest, and to carry out this routine week by week until the patient is apparently quite well or until a partial remission is achieved and the further continuance of the insulin treatment fails to bring about a progressive response. The time usually occupied for this is ten weeks, but certain patients recover in from four to seven, while others, in whom it may be difficult to induce coma, may take as long as fourteen weeks before the treatment is complete. It is usually considered advisable to induce about twenty insulin shocks before deciding that a patient who has during these shocks shown no favourable response, is unsuitable for such treatment. In the favourable cases treatment is usually terminated slowly by decreasing the amount of insulin for several days. It is sometimes possible after a number of attacks of coma to reduce the dose of insulin and still make it effective. With patients who seem to have an abnormal resistance to insulin it has been found that coma may be produced by varying the dose in a zig-zag fashion from day to day.

While a considerable number of patients are able to gain complete remission of their symptoms, it has been found that a small percentage of these are likely to suffer relapse at a later date. It would seem that certain schizophrenic patients are so severely handicapped in their situation that they are unable to face reality under the conditions of their social environment, and it is these who are liable to relapse; for a doctor, while able to modify mental and physical conditions in the patient, is unable in most instances to bring about any appreciable change in the environment to which he must become adjusted if he is to remain well.

Convulsion Therapy.

"Cardiazol."

Following quickly on the introduction of insulin in the treatment of schizophrenia came the knowledge that epileptiform convulsions artificially induced had a beneficial effect similar to the shock produced by insulin. This discovery wase made by von Meduna in Budapest. He elaborated his treatment on theoretical considerations and then sought to find a convulsant drug capable of easy, painless and rapid administration. His experiments, carried out initially with camphor, finally led to the use of "Cardiazol", and this drug has gained the widest acceptance in the psychiatric world in the last three years. Its therapeutic application is not confined alone to schizophrenic patients, but is equally beneficial in the affective states, particularly in states of melancholia and stupor.

"Cardiazol" is given in a 10% solution by the intravenous route. The usual convulsant dose is five cubic centimetres, but higher doses are frequently necessary to provoke the convulsion, and a patient who at the beginning of treatment may have a satisfactory convulsion with five cubic centimetres, may require six, seven or eight cubic centimetres as the treatment proceeds. The "Cardiazol" must be given with sufficient rapidity, otherwise no convulsion will occur. The patient should not have previously been given any anti-convulsive drugs, particularly bromide or any of the barbituric acid derivatives. The only sedatives permitted prior to convulsive treatment are paraldehyde or morphine and hyoscine. The convulsion which follows the injection of "Cardiazol" occurs within a few seconds and is to all outward appearance similar to a major epileptic fit. The patient's clothing is loosened at the neck, and a tampon is placed between the teeth during the tonic stage of the fit, when the mouth opens in a convulsive spasm. The clonic stage is followed frequently by a short period of apnœa, and this in turn is followed by the stertorous breathing of post-consulsive coma.

Meduna makes it a practice to induce a convulsion every third day; but there is no hard and fast rule in this regard, and much depends on the patient's mental condition. Personal experience has led to the giving of "Cardiazol" every other day at the commencement of the treatment and to the gradual lengthening of the period between injections up to about five days as the patient's mental condition improves. After each fourth or fifth injection therapeutic conversation with the patient is undertaken. Simple explanations are given and some attempt is made not only to establish the patient's contact with reality, but also to understand the personal problems which may have helped to precipitate the psychosis. Exercise, visits from friends and occupational therapy are utilized as soon as the patient is judged to be capable of deriving benefit from them. It is essential that the injection of "Cardiazol" should produce a convulsion; otherwise the patient is liable to be made worse on account of the unpleasant subjective experience and hallucinations brought about by the injection. If, therefore, the injection of "Cardiazol" fails to produce a convulsion within a minute or so, a second and larger dose of "Cardiazol" must be administered. This has no detrimental effect on the patient other than in a few cases to produce a tendency to post-convulsive vomiting.

Contraindications to "Cardiazol" Therapy.—The contraindications to the use of "Cardiazol" therapy are as follows: (*a*) Age. No limit has been fixed for the exact age beyond which this form of treatment should not be given. Patients of over sixty years have been known to withstand the rigour of convulsion therapy, so that it would appear in this connexion that physical health is more important than age. (*b*) Organic diseases of the cardio-vascular system. On general grounds one would advise caution in the application of this form of treatment to a patient whose heart's integrity was in doubt. Evidence of advanced arteriosclerosis is a definite contraindication, but a moderately elevated blood pressure is not of itself a barrier to treatment. (*c*) Febrile and inflammatory states. (*d*) Pregnancy. (*e*) Active tuberculosis. (*f*) Exophthalmic goitre. Exophthalmic goitre in mild form is not necessarily a contraindication, but cases in which it is present should be judged on their merits. (*g*) Diseases of the kidneys and the blood. Diseases of the kidneys and blood require thorough investigation by both clinical and laboratory methods before treatment may be undertaken. Again each condition must be judged on its merits. (*h*) Syphilis. Syphilis of the central nervous system is a definite contraindication. Debility may call for caution, but barring the liability to fracture, debilitated patients often undergo convulsion therapy with remarkable unconcern. Indeed, the introduction of this type of treatment often marks the beginning of an all-round improvement in general health.

Accidents and Dangers.—In the many thousands of artificially induced convulsions now on record, there have been few serious accidents and remarkably few deaths. Deaths have been due to unsuspected and undiagnosed physical disease, and experience shows very clearly that, if properly administered, convulsion therapy is a relatively safe procedure. Fractures and dislocations are the commonest of the accidents. Subluxation of the jaw is frequently encountered and may be prevented by holding the jaw during the fit. Dislocation of the shoulder occurs occasionally, and occasional cases of fracture of the scapula, humerus, femur and vertebræ have been reported. Patients sometimes tear some muscle fibres in the back, and herniæ have been produced in a few asthenic elderly patients.

"Triazol".

"Triazol" (cyclohexyl-ethyl-triazol), known commercially as "Azamon", was introduced some time later than "Cardiazol" by Walk and Mayer-Gross, who claimed that it possessed certain advantages over "Cardiazol". These advantages were that a much smaller dose could be used, that the rapidity of the injection did not matter, that there was less preconvulsive apprehension and that it was a more reliable drug for intramuscular use. The indications, contraindications, accidents and dangers are the same as those already specified for "Cardiazol". The time that elapses between the giving of the injection and the onset of the convulsion is longer with "Triazol" than with "Cardiazol", and during this period the patient frequently develops myoclonic jerkings, which gather intensity and lead into the convulsion. The post-convulsive amnesia seems more complete with "Triazol" than with "Cardiazol", and patients generally who have had experience of both drugs are inclined to prefer "Triazol".

Electro-Shock Therapy.

The latest method introduced by Sogliani for the production of artificial convulsions is electricity, which can, of course, be controlled more easily than any convulsant drug. The convulsive phenomena are similar to those produced by "Cardiazol". It is said that several fits may be produced in fairly quick succession without danger and before the patient regains consciousness. It is further claimed that the post-convulsive excitement sometimes produced by chemical convulsants is not found after electrically induced fits. This method is relatively new, but the results so far claimed for it resemble those achieved by convulsion therapy in general.

Results—Good and Bad.

Whatever the convulsant drug used, treatment should be carried on until the patient has recovered or until no further improvement can be brought about. The tendency is to terminate the treatment too early, with the result that the patient, after having obtained a good remission, is liable to relapse. If this happens, a further course of convulsion therapy should be given, but to avoid its happening, it is wise to carry on and to give at least three convulsions after the patient has gained a remission. In cases in which no favourable response is obtained, it is wise to give at least fifteen convulsions before deciding that the treatment is of no avail.

Extravagant claims have been made by some psychiatrists for the value of convulsion therapy. In general, the number of remissions achieved by this method in schizophrenia is approximately the same as may be obtained by insulin shock. The best response is always in the earlier cases. Artificially induced convulsions often prove beneficial in the affective psychoses by shortening the period of depression or elation to a considerable extent; but the treatment appears to have no value in checking the periodicity of manic-depressive states.

Undesirable results are sometimes encountered. Depressed patients, following convulsion therapy, may become violent and agitated for prolonged periods; and further induced convulsions only render the condition worse. If, therefore, such an untoward reaction occurs, the convulsive treatment must be terminated and the patient given a course of insulin therapy or quietened with continuous narcosis. Again, unaccountably and regrettably, some patients show an insidious mental deterioration as the convulsion therapy proceeds. This reaction is rare, but difficult to guard against. Should there arise any suspicion of deterioration during treatment, it is essential to call a halt lest irreparable damage be done to the nervous system.

Conclusion.

In these encouraging yet empirical forms of treatment what may be one person's meat is another's poison. Ignorance shrouds the biological changes brought about by pharmacological shock as it does the psychological mechanisms involved in the illness and its remission. Experience shows a different response in similar patients: that where insulin fails, "Cardiazol" may succeed or *vice versa*. Consequently, although a large number of patients have been and are still being successfully treated by one or other method, it has become a common practice to combine the treatments. This combination has definite advantages. Its great merit is that as the convulsant drug is given during the insulin coma, the patient is saved the anxiety and distress which invariably precede the convulsion. Insulin may also act as a sedative in disturbed patients and is often invaluable in improving the general health and physical fitness.

The danger of convulsion therapy lies in the simplicity of its administration, in the psychiatrically inept practitioner who may welcome it as the cure-all to the detriment of many patients. Experience alone can teach how and when to use induced convulsions, and how and when they may with advantage be combined with insulin. And such experience is in some ways similar to the wisdom displayed when "angels fear to tread".

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British Medical Association News.

SCIENTIFIC.

A MEETING of the Victorian Branch of the British Medical Association was held on August 7, 1940, at the Medical Society Hall, East Melbourne, DR. H. C. COLVILLE, the President, in the chair.

Some Recent Contributions of Anatomy to Medicine.

PROFESSOR SYDNEY SUNDERLAND discussed some recent contributions of anatomy to medicine. He pointed out the difficulties involved in the selection of suitable material for a lecture such as the one he had undertaken. He indicated that it was unlikely that any contributions made by anatomy would have the dramatic and revolutionary effect such as one found in other fields, as, for example, recent advances in chemotherapy. Moreover, it was obvious that research in anatomy, with its fundamental biological implications, would involve many contributions which did not touch directly or immediately on the practice of medicine—the so-called academic contributions which, nevertheless, might considerably influence future advances in the field of practical medicine. In the absence of the dramatic, the slow infiltration of new and beneficial ideas was likely to pass unnoticed. A careful analysis of the relevant literature would, however, instantly reveal the many contributions which had filtered into medicine from anatomical laboratories in recent years—contributions whose importance would increase in significance with the passage of time. These contributions were so numerous that the great difficulty had been to restrict the field and to select only that work would would prove most interesting.

The first subject chosen was the influence exerted by sex hormones on the embryonic differentiation of the genital tract, because knowledge gained from such investigations had provided a better understanding of many forms of clinical intersexuality. Professor Sunderland first stressed the fact that the discovery that chemical agents could modify and control the development of organized structure was a very recent addition to biological knowledge. The development of such a concept was traced from the principle of dependent differentiation introduced by Roux, to the work of Spemann on the influence of the organizer or inducer on developing tissues, and then to the discovery that organizers could act after their cells had been coagulated and killed. Subsequent analysis had demonstrated that the substance responsible for such action was related to the sterols—a fitting introduction to investigations dealing with the action of sex hormones on the developing genital tract.

The first striking demonstration that sex hormones might be concerned in the embryonic differentiation of the genital system was provided by the free-martin, a curious developmental anomaly found in cattle twins, in which one of the new-born possessed a mixture of male and female features. It was well known that in cattle twins, when the fœtal membrane of male and female embryos were so united that a well-developed cross-circulation or anastomosis was present between the two, then the female was found to be modified in the male direction, forming the so-called free-martin. If there was no anastomosis or cross-circulation, then the female was normal. Lillie was the first to suggest that this sex reversal was produced by the sex hormones secreted from the male co-twin. This hypothesis that the free-martin was possibly a female modified in the male direction by the action of sex hormones from a co-twin male embryo initiated an era of experimental study on the mechanism involved in such a transformation.

Professor Sunderland next surveyed the experimental investigations undertaken in connexion with this problem, commencing first with the work on amphibian parabiotic twins and with studies on the action of sex hormones on the developing chick embryo. It was shown how such work substantiated the belief that sex hormones could influence the development of the genital tract. It was explained that such experiments were of the simplest type, because in amphibian and chick embryos the complete isolation of the embryo during development removed any difficulties introduced by a host which was itself secreting hormone. Experiments on mammals were later in their appearance because of this complicating factor. Dantchakoff was the first to subject the developing mammalian embryo to the action of sex hormones. She injected the hormones directly into the amniotic sac of developing guinea-pig embryos. This work was followed by the investigations of Greene, Ivy and others, who injected the hormones into pregnant mice and rats, and, lastly, by those of Burns, who injected the hormones directly into the pouch young of the opossum. The results of these workers were then outlined and summarized. Certain paradoxical effects obtained were discussed; but despite these it was shown that there was sufficient evidence to indicate that sex hormones exerted some control over the development of the genital tract. Though the problem could by no means be considered as solved, it would appear from such work that development in the genital tract probably took place somewhat in the following way. The genes were the effective agents in the early stage of male and female differentiation, so that the conversion of the indifferent gonad to an ovary or testis was the property of the genes and was not under endocrine control. The Wolffian and Müllerian ducts and the ambisexual urogenital sinus developed in both sexes and their earlier differentiation was not under endocrine control; their subsequent development, however, depended upon the direction taken by the gonads. If the gonads became testes, these secreted male hormone, which stimulated the Wolffian duct derivatives and suppressed the development of the Müllerian duct derivatives. If they became ovaries, then these secreted female hormone, which stimulated the Müllerian duct derivatives and suppressed the Wolffian duct derivatives. Superimposed on this fundamental pattern were the secondary sexual and psychological changes occurring at puberty. Thus sex hormones in no case caused the development of any new structure, but merely stimulated or suppressed parts already laid down. On the basis of such work a more rational explanation of many of the anatomical abnormalities encountered in cases of intersexuality was then put forward.

Professor Sunderland, in conclusion, referred to some recent advances in neuro-anatomy; he outlined accounts of detailed studies on the spinal nucleus of the fifth cranial nerve, upon which was based a new operation for the relief of pain in the face. This aimed at the production of a dissociated anæsthesia of the face, eliminating pain and temperature sensation, but preserving the other sensory elements. The anatomy of spino-thalamic pathways in the cord and their relationship to chordotomy were discussed, and finally the role of hypothalamic centres in temperature regulation and their control of water metabolism in the body were briefly surveyed.

DR. ROBERT FOWLER expressed warm appreciation of Professor Sunderland's address, which, he said, disclosed an authorship prepared to look beyond the cell as the unit of anatomical structure and an ability to think of "the stuff we're made of" in terms of molecules and atoms. By applying these ideas to embryology the lecturer had revealed the drama of human development in a new light; as the action unfolded it was realized that these amazing anatomical changes were based upon a series of physico-chemical episodes. In other words, ontogenesis—the development of the individual—had a physico-chemical basis. Professor Sunderland had suggested a useful generalization, namely, that Spemann's organizers, which were active during the totipotent stage of development, were much the same chemically and physiologically as the specialized hormones which later replaced them. This simplification meant that, primarily, all living cells were endowed with a capacity for secreting locally acting chemical regulators, but that, as development proceeded, the function of chemical regulation by internal secretion was reserved first to certain tissues of the segment and finally to certain organs of the soma. Through the sex hormones the faculty of chemical regulation was transmitted by way of the genes to successive generations, so that they arrived at the conclusion that phylogenesis, as well as ontogenesis, had a physico-chemical basis.

This line of thought implied that the sterols constituted one of the most important chapters in biochemistry. Whether that was so or not, there was no doubt that a study of the sex hormones was of extreme importance to the practising gynæcologist. It was well, therefore, to recall some of their fundamental characteristics. To begin with, most ductless glands were common to all orders of vertebrates, and a glandular extract from one order would usually exert its specific effect when administered to a member of another order. That fact had made possible a wide range of organotherapy, out of which synthetic hormone therapy had sprung. Another feature to be noted was the relatively small size of a hormone molecule. In 1902, when Bayliss and Starling discovered secretin, Starling immediately jumped to the correct conclusion that this substance had a low molecular weight. He was led to this assumption by the rapidity of the secretogogue effect, by the absence of antigenic properties, and later by the observation that secretin withstood a temperature of 110° C. without prejudice to its effect upon the pancreas. That there was no antibody formation following injection of chemically pure hormones was a highly significant prerequisite of hormone therapy. They still lacked an explanation of the refractory state that sometimes followed repeated injections of a hormone, an explanation of how a hormone became used up, and an explanation of the synergic action of hormones. All those questions were important when the dosage and the interval of administration were being determined.

Dr. Fowler went on to say that the practising gynæcologist had occasion to deal surgically with some of the developmental anomalies mentioned by Professor Sunderland. He referred to congenital absence of the vagina, or, more correctly, atresia of the vagina and uterus. This anomaly, when observed in adults, appeared to afflict women with otherwise normal psyche and physique. Not unusually they contracted romantic attachments and were thereby placed in a dreadful dilemma, which occasionally resulted in

suicide. Dr. Fowler had observed nine patients—seven in his own practice, one for whom Dr. Felstead, of Horsham, had performed a successful Schubert's operation, and one in Berlin, for whom Professor Wagner had performed his own operation. The Schubert operation aimed at creating an artificial vagina from an isolated segment of the rectal ampulla; the integrity of the alimentary canal was restored by bringing the proximal portion of the colon down through the anal canal. The Wagner operation aimed at the Thiersch grafting of a cavity created by dissection from below through the areolar tissue separating the bladder from the rectum. Blunt dissection of this area presented no difficulty after a circular area of mucosa in the hymenal region had been denuded; as a rule, when the correct tissue plane had been defined, the dissection could be carried up to the peritoneum of Douglas's pouch. Wagner had designed a cylindrical prosthetic apparatus of appropriate dimensions consisting of sponge-rubber mounted on a rigid stem. When dressed with broad strips of epidermis, cut with the Kirschner machine, this prosthetic apparatus was placed as an obturator in the vaginal cavity and secured in position for ten days. After removal regular post-operative dilatation was necessary. Dr. Fowler's personal experience had been confined to the performance of Baldwin's operation—a brilliant and daring conception, which was eminently satisfactory in its results. The aim of the operation was the creation of an artificial vagina from an isolated loop of ileum with its mesentery intact—the most ambitious form of pedicle grafting. Dr. Fowler had not seen the Frank-Geist operation of "satchel-handle" skin grafting. In all the operations mentioned, a dissection of the tissue between rectum and bladder was a necessary preliminary. In recent years success was reported to have followed intermittent pressure from below with graduated dilators without any grafting of tissue or viscus. It was stated that after the initial attrition an epithelialized fossa developed, which through perseverance gradually became enlarged to the requisite size. Confirmation of this work would naturally relegate all grafting operations to the past. The biological mechanism whereby tissue differentiation occurred during this procedure took those present back to the physico-chemical considerations with which they started.

DR. A. E. COATES said that he was grateful for the privilege of taking part in the discussion after such a lucid presentation of the subject by Professor Sunderland. As one interested in the anatomy school, he welcomed the opportunity of greeting Professor Sunderland and congratulating him on his address. Professor Berry, who had held the chair of anatomy at Melbourne, had once remarked to him (Dr. Coates) that during the last war, when things looked black, the British Prime Minister called upon three men to take charge of important departments; they were Sir Auckland Geddes, Sir Eric Geddes and Dr. Addison. They were all anatomists. Perhaps the flair for detail and precision which characterized the anatomist were valuable assets in public men controlling departments. Professor Sunderland, who had received his training at Melbourne, was a worthy successor to Professor Wood Jones.

Dr. Coates said that he could not contribute much to the discussion of the sex hormones. In fact a critic, if present, might even suggest that the discussion was already degenerating (with apologies to Professor Wright) into a physiological one. However, all that went to show that anatomy could no longer be regarded as simply the science of description of macroscopic structure, but that its interests went far beyond, into the realm of biochemistry. Anatomy and physiology thus were no longer divided, but both were the one language. Perhaps anatomy might be regarded as supplying the nouns, and physiology the verbs. They were one and indivisible in the same language; the study of one without the other was impossible. So Professor Sunderland's approach to the structural problem in his address was hormonal (physiological). Function came before structure, and in fact determined structure, and thus the two sciences were complementary. There appeared to be little research remaining to be done in anatomy; critics maintained that it was a worked-out science. However, that was not so. As in geography the main continents and oceans had been discovered and explored, the peaks surveyed, so in anatomy the outlines of macroscopic structure had been described in detail. In histology most of the structures of the body had been stained and examined by the means at their disposal, and accurately described. It might be that other methods of staining and perhaps quite different and at present unthought-of methods of study of those tissues would reveal structural secrets of which they at present had no hint. There was, however, a no-man's-land which lent itself readily to exploration and which was not well known. How many students had examined the gall-bladder lining with a magnifying glass of six diameters? There were many small nerves in the body, such as those which passed to blood vessels, which were too small for the naked eye. Much useful research was yet to be done in that field, to describe the minute structure just beyond the reach of unaided vision, but yet not within the range of the microscope. Contributions to studies in that field had been made by clinicians and surgeons. One such contribution in their own school was that by Dr. Hugh Trumble on the nerve supply of the colon. Trumble's nerve had now found its way into the literature. Not infrequently experimental surgery needed to turn back to elementary anatomy, and the latter science was enlarged or corrected in some detail which hitherto had been regarded as unimportant. The recent developments in the use of opaque media for the radiological examination of arteries and veins, for the detection of aneurysms and arterio-venous communications, had shown that the living artery was not quite of the same configuration as that found in the cadaver. Conversely, varicose veins which did not respond to injections might be found on closer examination to be really arterio-venous channels representing the primitive embryonic network, never having progressed to form the complete arterial and venous trunks. Again, surgery had much to learn from anatomy. What sort of surgery was possible without a thorough knowledge of normal structure and relations? But that was not enough; there had to be an appreciation of the abnormal—morbid anatomy. Fortunately for the human race, surgical anatomy was illustrated in the walling-off of tumours, such as the hypertrophied prostate gland; it rendered the enucleation of the diseased part a simple matter. They should compare the mess that would follow a similar attempt with a normal gland. The fascia of the neck, to which attention had recently been directed by Dr. Meyers, of Brisbane, was an important structure, its divisions and attachments playing a major part in the spread or arrest of purulent collections. The dilated common bile duct was easy to find; the third ventricle tumour could be removed through the dilated lateral ventricle of the brain. Pathology altered anatomy, and those alterations had to be duly appreciated. Radiology had done its share in clearing away many preconceived ideas of the normal form and position of organs. The long, low, hanging stomach was not regarded as necessarily abnormal, any more than the long protruding nose. Much valuable data had been added to their knowledge of the abnormalities of skeletal structure as well as visceral deformities which were quite compatible with health and happiness.

Dr. Coates then referred briefly to the nervous system. He said that he had yet to learn of a certain method of curing chronic non-paroxysmal pain in the face. Apart from *tic douloureux*, which was readily cured by root section or ganglion destruction, other pains in the face were most difficult to relieve. Nature seemed to make sure that primitive nociceptive impulses did reach the thalamus by some route or other. In the face there were multiple pathways apart from the fifth nerve for those impulses to reach the appropriate centres. Perhaps the new operation of tractotomy would cure many of those patients; it was doubtful whether it would cure all. With regard to spinal cord tracts, Dr. Coates said that he had divided the spino-thalamic tracts at the level of the fourth dorsal segment for intolerable pain in an amputation stump of the leg on the same side. Complete relief was obtained. If, as Professor Sunderland had said, those pain fibres diverged in the cord, it must be at a higher level than the segment mentioned.

In conclusion, Dr. Coates said that any description of advances in anatomy should include the detailed work on the hand spaces, more especially that of the late Professor Alan Kanavel. To those with a taste for good literature, he recommended a book by Professor Sunderland's predecessor, Professor Wood Jones—"The Principles of Anatomy as Applied to the Hand". The Melbourne school of anatomy had been fortunate in the past in the occupants of the chair; Halford, Allen, Berry, Wood Jones were names to remember. Those men had left their mark there. Melbourne graduates going overseas found that their reputation as anatomists had preceded them. The tradition of the school was well known abroad. It was certain that that reputation would be maintained and enhanced by the present occupant of the chair, Professor Sydney Sunderland.

DR. H. C. COLVILLE welcomed Professor Sydney Sunderland. He said that as Professor Wright, professor of physiology, had addressed a meeting of the Branch in March, 1940, those two gentlemen had demonstrated in an eminently practical manner their willingness to discuss matters of mutual interest with members of the Branch; that attitude was greatly appreciated by the members.

DR. JOHN S. GREEN briefly discussed the possible effects of the maternal hormones on the developing sex organs. He assumed that the undifferentiated sex cells had their actual sex predetermined by the nature of their chromosomes. The sex cells as they became differentiated might

vary in their reactivity to maternal hormones. Moreover, the maternal sex hormones had ambisexual effects, and there could be the various combinations of potential male organs or potential female organs subjected to both gynæcogenic and androgenic factors. In the circumstances it was surprising that intersexual development was so rare. Dr. Green raised one clinical point, that patients under treatment for sterility had become pregnant when receiving moderately large doses of œstrogen. As the œstrogenic effect would presumably be operating at a very early stage in the pregnancy, he wondered whether the child, if it was a male, would be likely to develop any female characteristics.

PROFESSOR MARSHALL ALLAN reminded the members of the interest Professor Wood Jones, Professor Sunderland's predecessor, had taken in the mysteries of development. They had heard the views of the mechanical school and of the vitalists; but Professor Sunderland, who had presented his facts in a very facile way, introducing the genes and the endocrines, appeared to belong to what might be called the neo-vitalist school. Professor Marshall Allan ended by drawing attention to the undeniable fact that there remained many gaps in the knowledge of the subject under discussion.

DR. F. P. MORGAN commented on Professor Sunderland's happy selection of subjects, which he had placed before the meeting in a manner clearly to be understood. Dr. Morgan had had experience of the operation of chordotomy in the upper thoracic region and pain had been abolished in the lower limbs; he had not found it necessary on any occasion to extend the incision as far posteriorly as Professor Sunderland had indicated. It would be of interest to members to know that by the use of the new operation for the relief of pain in the face, the tactile sense was preserved on the face, including the cornea.

DR. H. C. COLVILLE, when calling upon Professor Sunderland to reply to the discussion, referred to a patient with hermaphroditism who had been under his care and observation for many years. At the age of two years the patient appeared to be a normal female with swellings in the inguinal regions. One of the swellings was removed and found to be a testis, and later the other was removed also. The patient had a "sister" with a similar condition, and Dr. Colville remarked that the mother must in some way have been the source of an excess of gynergen. Dr. Colville's patient had come to him recently for advice, as she proposed to marry. He concluded his remarks by observing that undescended testes were non-functioning testes, and yet many surgeons operated to replace them in normal position.

Professor Sunderland, in reply, thanked the speakers for their interesting and informative comments and for introducing and amplifying additional features which he had either omitted or had only briefly mentioned, for these had added considerably to the scope and interest of the lecture. He believed that the many practical points of clinical interest which had arisen in the discussion were additional proof that recent work in anatomy did have a very real and material bearing upon the problems of clinical medicine.

In answer to Dr. Green's inquiry concerning the possible effect on the developing male embryo of female hormones injected therapeutically into the pregnant mother, Professor Sunderland stated that the permeability of the placenta to the hormone and the concentration reached in the developing embryo were the all-important factors. Normally male embryos developed undisturbed in a host in which œstrogen was the predominating, if not the sole, sex hormone present. A high œstrogen level in the parent, however, did not necessarily mean a high œstrogen level in the fœtus, whilst it was not yet definitely established that the œstrogen from the parent was directly responsible for the modification of the differentiating male elements in the female direction in human pseudohermaphroditism, even though such changes could be produced experimentally by the injection of œstrogen directly into the embryo or by the overloading of the parent with this substance. If the œstrogen of the host were responsible in humans, then the factor which upset the relationship between the differentiating male genital tract and the circulating œstrogen was as yet unknown.

Concerning Dr. Colville's inquiries relating to the function of undescended testes, Professor Sunderland believed that any testis remaining in the abdominal cavity or returned to it became sterile, and that such retained testes could even secrete œstrogen, which might be responsible for certain feminizing effects observed in such cases. The unhappy lot of the intersexual and the very real problem which they presented with regard to treatment were the subject of comment of the majority of speakers that evening, and Professor Sunderland emphasized that the solution of those problems demanded the closest cooperation between anatomist, endocrinologist, biochemist and clinician.

Many additional features had been introduced in the discussion which deserved comment; but he appreciated that a full discussion on such a contentious problem could be almost endless. The motive for the survey of such a field as that chosen was to emphasize that anatomy was not a science of statics dealing solely with dead organisms, but that it was a science of dynamics dealing with all biological phenomena relating to structure and the regulation of structure, and that at least some of its contributions had a real and direct bearing on clinical medicine.

Medical Societies.

THE MEDICAL SCIENCES CLUB OF SOUTH AUSTRALIA.

A MEETING of the Medical Sciences Club of South Australia was held at the University of Adelaide on June 7, 1940.

Aphasia.

DR. H. K. FRY presented a paper on aphasia. He stated that Broca's description of a speech centre was followed by an era of diagrams which explained the phenomena of aphasia in terms of the supposed existence of four cortical centres presiding over articulation, writing, auditory word images, and visual word images. Marie's redescription of the brains of Broca's patients helped to establish more reasonable ideas. The writings of Pick and Head confirmed and amplified the physiological principles expounded by Hughlings Jackson. Jespersen in particular had explained the probable nature of primitive speech. *Gestalt* psychology probably had given the best explanation of the basis of perception as a pattern of sensory stimulation. The Freudian school of psychology had explained the nature of the dynamics of mental processes.

Bacterial Degradation of Cellulose in Sheep.

MR. E. W. LINES described the results of some of his work (carried out in association with Mr. F. V. Gray) on "Bacterial Degradation of Cellulose in Sheep".

Mr. Lines pointed out that the sheep maintained a very active flora in its anterior stomach, which split insoluble polysaccharides, such as cellulose, into digestible fragments. The fermenting mass might weigh as much as 20% of the animal—about seven to eight litres in a 40-kilogram sheep. In this apparatus 400 to 500 grammes per day of cellulose could be degraded mostly to fatty acids. At the same time, up to 100 litres of gas were evolved. Of this volume, 20% was methane, 40% to 50% arose from salivary carbon dioxide, and the remaining 30% to 40% from the fermentation.

The ratio of methane produced to cellulose degraded was labile and probably arose from the activity of a separate variety of bacteria.

The medium for the culture was mostly parotid saliva, of which eight to ten litres per day were produced by a sheep. Inorganic media made to resemble saliva were satisfactory to rumen culture. There was much evidence to suggest that bacterial growth hormones were necessary for the activity of the bacteria. Yeast and lucerne were good sources of bacterial growth hormones, grain was fair, hay and straw were poor.

Special Correspondence.

CANADA LETTER.

BY OUR SPECIAL CORRESPONDENT.

THERE is more than one reason why it is not easy to keep up correspondence in these days. For one thing, the overwhelming absorption of all interest into the one thing that everyone is thinking of; for another, the dislocation of ordinary routine by the changes in conditions; for another, the need to consider censorship.

However, these things should not be enough to enforce silence permanently.

I suppose, in your country as well as in ours, no profession has had to rearrange the work of its members

more than has medicine. This is most apparent, of course, in the large hospitals, where the loss of personnel has been most marked; but it applies also to some extent in the country parts. In one large hospital in Montreal alone, not less than 52 members of the staff are in uniform. That leaves little more than a skeleton to carry on not only the ward work, but the teaching. So far, however, there has been no insuperable difficulty. The men did not leave all at once, and some readjustment of work was necessary. No special arrangement has been made for the conduct of the practices of those who have gone into the army. As in the last war, men have left their work and hope to pick up some of it when they get back. A suggestion was made by one Province that men might be permitted to enlist for limited time service overseas, with the further suggestion that the period of time be one year and that at the end of that time reenlistment might be possible. The reply to this from headquarters, however, was that men could be recalled on reasonable grounds, but no general ruling could be given applicable to all enlistments.

There is also great difficulty in getting orderlies for the hospital work. They have always been drawn from a transient type of labour, but now most such men are in the army. Lately some relief of the situation has been obtained by having squads of men from various hospital units come in for training in hospital work.

X-Ray Examinations of Recruits.

About two months after war broke out it was decided that X-ray examinations of the chest of every soldier would be put into force. This took a good deal of doing. In the last war it could never have been arranged, for the profession then did not realize how totally inadequate the average chest examination is for revealing pulmonary disease, even in fairly advanced stages. Now we do realize this, and we have been able to persuade the Government that routine X-ray plates are going to save millions of dollars in the long run. It was calculated that the cost for the first hundred thousand men would be about $200,000, as against the many millions which would certainly be paid out by the country in pensions otherwise.

Of course it is not only the lungs about which X-rays give such valuable information. The size of the heart can also be judged, and with an accuracy far beyond that attained by percussion.

Two main points had to be given consideration. Was the admittedly large problem of arranging for such large numbers of X-ray examinations going to interfere seriously with the heavy work of rapid mobilization? Was it going to result in such a close combing out of potential disease that recruiting would be hampered?

The answer to these objections was: (*a*) The effort of administering the survey would be more than outweighed by the rejection of recruits before they became administrative problems for treatment, transportation home, and replacement, when after months of training they arrived at a theatre of war. (*b*) It was felt that the rejection figures would not exceed 2%, which is pretty small compared with the rejections based on dental defects, eye trouble, and other lesions of less serious nature than thoracic disease. It was also to be remembered that the removal of men with early tuberculosis at the outset would prevent a certain degree of infection from being passed on to their comrades.

The results have more than justified the plan. As had been thought, the total rejection on X-ray findings was less than 2%. This included circulatory as well as respiratory disease, with tuberculosis, of course, in the forefront. Quite apart from the financial and administrative value of these X-ray examinations, they have served to bring out many interesting points. They have proved beyond any question at all, if any such proof were needed, that the X-ray examination will reveal the most extraordinary degrees of pulmonary disease of which there is no clinical evidence, or at any rate non-detectable on one examination. From a public health point of view also the examinations are invaluable. Finally, there is an appreciable saving in time in making examinations.

Of course there are problems in carrying out this work. What, for example, is to be done about the minimal, apparently healed lesions, which are so numerous? In such cases the lesion itself was not regarded as ground for rejection. Efforts were made to assess the likelihood of such lesions breaking down on service. Other things being equal, recruits with these were accepted. Lesions of greater extent, and with more doubt as to their stage of healing, were passed on to specialists for further study, and then given a lower classification. Quite probably a few of these selected minimal healed lesions will break down on active service, but not enough of them to invalidate the general methods. One surprising thing brought out by the survey was the number of ambulatory cases of both lobar pneumonia and bronchopneumonia.

Correspondence.

THE CONTROL OF WHOOPING COUGH.

SIR: May I congratulate you on publishing in your issue of November 16, 1940, the excellent article by Dr. Dorothy Gepp on pertussis immunization, and also on your leading article in the same issue. The public and even some of the profession do not realize the dangers of this disease, especially in the infancy period, and it is to be hoped that in the near future a campaign can be instituted in this State to achieve protective immunization in the latter part of the first year of life.

In the meantime much can be done to educate the public in the need for segregation of sufferers with the disease and also of contacts who have not had an attack. This particularly applies to public conveyances, beaches, picture shows and also doctors' surgeries. Education is also needed in the disposal of the phlegm and vomit from this disease. Steps are being taken to have this done in the near future, but practitioners can do a lot in this matter.

Yours, etc.,

LINDSAY DEY.

British Medical Association House,
137, Macquarie Street,
Sydney.
November 17, 1940.

SCEPTICISM AND AUTHORITY: A REPLY.

SIR: Your leading article on November 23 tempts me to apply the principle of scepticism to the article itself. For although you advocate a critical survey of authority, a policy which is always worth while, your leader resolves itself into a didactic statement, itself authoritative in tone.

The article lays down that the only way of increasing effective knowledge is by the method of working hypothesis, prediction and trial, all on the basis of a series of observations. This is an authoritative statement which I challenge. The rigid application of the "scientific method" of arguing from the facts towards the theory may be admirable for many practical problems, but in my opinion it is a brake upon new ideas.

Granted that any idea must ultimately pass the test of clinical trial, I am strongly of opinion that the less scientific but more imaginative method of arguing from the theory to the facts is far more likely to take us into unexplored territory and open up new ground.

What real advance, for example, has dissecting the known facts achieved in the problem of cancer?

Yours, etc.,

A. W. D'OMBRAIN.

17, Bolton Street,
Newcastle,
New South Wales.
Undated.

Naval, Military and Air Force.

APPOINTMENTS.

THE undermentioned appointments, changes *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*, Number 232, of November 21, 1940.

PERMANENT NAVAL FORCES OF THE COMMONWEALTH (SEA-GOING FORCES).

Appointment.—Surgeon Lieutenant Kingsley Edric Fenton Dixon Hudson, Emergency List, is appointed for temporary service, dated 1st November, 1940.

CITIZEN NAVAL FORCES OF THE COMMONWEALTH.

Royal Australian Naval Reserve.

Termination of Appointment.—The appointment of Surgeon Lieutenant-Commander David Aubrey Arnot Davis is terminated, dated 20th August, 1940.

AUSTRALIAN MILITARY FORCES.

SOUTHERN COMMAND.

Third Military District.

Australian Army Medical Corps.

Honorary Captain C. E. Willing is appointed from the Reserve of Officers (A.A.M.C.), and to be Captain (provisionally), with seniority next after Captain (provisionally) V. Brand, 18th August, 1940.

Australian Medical Board Proceedings.

QUEENSLAND.

THE undermentioned have been registered, pursuant to the provisions of *The Medical Act* of 1939, of Queensland, as duly qualified medical practitioners:

Shera, John Arthur McKelvey, M.B., 1939 (Univ. Sydney), General Hospital, Ipswich.

Ropschitz, Izydor, M.D. (Padua), St. Kilda Flats, Moray Street, New Farm, N.1.

Honours.

HIS MAJESTY THE KING has been pleased to approve of the following appointments.

Honorary Physician to the King: Surgeon-Captain William James Carr, C.B.E., Royal Australian Navy; Colonel Douglas Murray McWhae, C.M.G., C.B.E., V.D., Australian Army Medical Corps; Group-Captain Edward Alfred Daley, Royal Australian Air Force.

Honorary Surgeon to the King: Surgeon-Captain Leonard Darby, C.B.E., Royal Australian Navy; Colonel Roy William Whiston-Walsh, D.S.O., V.D., Australian Army Medical Corps; Air-Commodore Thomas Ernest Victor Hurley, C.M.G., V.D., Royal Australian Air Force.

Obituary.

STANLEY ARGYLE.

WE regret to announce the death of Sir Stanley Argyle, which occurred on November 23, 1940, at Melbourne, Victoria.

Medical Appointments.

Dr. J. R. McClean has been appointed Government Medical Officer at Barellan, New South Wales.

* * *

Dr. J. G. Hulme has been appointed a Medical Referee, in pursuance of the provisions of *The Workers' Compensation Acts*, 1916 *to* 1939, of Queensland.

* * *

Dr. J. Coffey has been appointed a Member of the State Council for Physical Fitness, of Queensland.

* * *

Dr. R. H. von der Borch has been appointed Honorary Assistant Aural Surgeon at the Royal Adelaide Hospital, Adelaide, South Australia.

Books Received.

"Handbook of Anæsthetics (formerly Ross and Fairlie)", revised by R. J. Minnitt, M.D., D.A.; Fifth Edition; 1940. Edinburgh: E. and S. Livingstone. Crown 8vo, pp. 378, with illustrations. Price: 12s. 6d. net.

"War Wounds and Injuries", edited by E. Fletcher, M.A., M.B., M.R.C.P., and R. W. Raven, F.R.C.S., with a foreword by Lord Horder; based on articles in the "Post-Graduate Medical Journal"; 1940. London: Edward Arnold and Company. Demy 8vo, pp. 270, with illustrations. Price: 14s. net.

"Medicine and Health in New Zealand: A Retrospect and a Prospect", by Douglas Robb; 1940. Auckland: Whitcombe and Tombs Limited. Demy 8vo, pp. 146. Price: 8s. 6d. net.

Diary for the Month.

DEC. 3.—New South Wales Branch, B.M.A.: Executive and Finance Committee; Organization and Science Committee.
DEC. 4.—Western Australian Branch, B.M.A.: Council.
DEC. 4.—Victorian Branch, B.M.A.: Annual Meeting.
DEC. 5.—South Australian Branch, B.M.A.: Council.
DEC. 10.—New South Wales Branch, B.M.A.: Ethics Committee.
DEC. 10.—Tasmanian Branch, B.M.A.: Branch.
DEC. 12.—New South Wales Branch, B.M.A.: Branch.
DEC. 13.—Queensland Branch, B.M.A.: Annual Meeting.
DEC. 17.—New South Wales Branch, B.M.A.: Medical Politics Committee.
DEC. 20.—Queensland Branch, B.M.A.: Council.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Honorary Secretary, 135, Macquarie Street, Sydney): Australian Natives' Association; Ashfield and District United Friendly Societies' Dispensary; Balmain United Friendly Societies' Dispensary; Leichhardt and Petersham United Friendly Societies' Dispensary; Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney; North Sydney Friendly Societies' Dispensary Limited; People's Prudential Assurance Company Limited; Phœnix Mutual Provident Society.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federated Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17): Brisbane Associated Friendly Societies' Medical Institute; Proserpine District Hospital. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178, North Terrace, Adelaide). All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205, Saint George's Terrace, Perth): Wiluna Hospital; all Contract Practice appointments in Western Australia.

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